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TRANSACTIONS OF THE XVth CONGRESS OF THE SCANDINAVIAN OTO-LARYNGOLOGICAL SOCIETY

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EDITORS

KAARE EIMIND · TORBJØRN NORDAHL

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MEETING OF THE COUNCIL OF THE SCANDINAVIAN OTO LARYNGOLOGICAL SOCIETY

The meeting took place in the Committee room of Rikshospitalet in Oslo, June 15th, 1963 at 12 o'clock

The following members of the Council were present at the meeting H Ewertsen, K Kettel, U Siirala, C-A Hamberger, A Sjoberg, T Leegaard, O Opheim, S Quist-Hanssen, E Steen and the Secretary of the Congress, L Lund Iversen

The President of the Congress, Professor O Opheim was elected Chairman

Professor U Siirala suggested that the next Congress should be held in Helsinki in 1966 The Council accepted the Finnish invitation with gratitude It was also proposed that the Congress committee for 1966 should consist of Professor U Siirala, President, Professor O Meurman, Vice president, Dr Goran Johnsson, Secretary This proposal was carried unanimously by the Council

The date of the Congress in Helsinki and the number of days required for it are to be determined by the Congress committee, who will also make up the program

The statutes of the Scandinavian Oto Laryngological Society were discussed The Council was agreed that some alterations were desirable It was determined that an amendment should be moved to the different societies for approval

It was decided that the annual subscription to the Scandinavian Oto-Laryngological Society should be raised by 10 Crowns in the currency of the country concerned, with, in the case of Finland, a free choice of Crown currency

For introductory lectures at the Congress the charge should be discussed in each case with the Editor

Business Meeting of the Congress

The meeting took place in the main lecture hall of Rikshospitalet, at the end of the afternooen session on Tuesday June 18th The President conveyed the Finnish invitation to the next Congress in Helsinki in 1966 and presented the Finnish proposal for the formation of the Congress committee The Congress accepted the invitation and agreed unanimously to the list of proposed members of the committee The date of the Congress and the extent and form of the program were left to the decision of this committee

The Congress confirmed the decision of the Council that the annual subscription to the Scandinavian Oto-Laryngological Society should be raised by

INDEX AUCTORUM

PATHOGENESIS AND TREATMENT OF ADHESIVE OTITIS

By

Urpo Surala

From the Otolaryngological Hospital University of Helsinki

Abstract

Adhesive otitis is an abacterial inflammation of the middle ear and the adjoining pneumatic spaces It has a tendency to become chronic and is characterized by occlusion of the Eustachian tube and formation of adhesions in the tympanum Three phases can be distinguished the early stage (middle ear secretion frequently mucous and changes reversible), the adhesive stage (inflammation still in progress), and the terminal stage (inflammation has subsided)

The incidence of adhesive otitis seems to be increasing The following factors may be responsible sulphonamide and antibiotic therapy, latent mastoiditis, and inadequate treatment of acute otitis media (neglect of myringotomy and air insufflation) During childhood in particular, some other factors, such as nasopharyngeal adenoids and sinusitis may also give rise to chronic otosalpingitis This condition unless properly treated, may lead to adhesive otitis

At the early stage therapy consists of conventional evacuation of secretion from the middle ear, and care is taken to obtain proper ventilation and tubal function. The formation of adhesions may result in disappearance of the middle ear air space Restoration of ventilation of the air space in the tympanum and of the sound conducting mechanism is possible in many cases by operation and medication The air space of the tympanum can be maintained by means of a polyethylene tube introduced through the operation wound or the Eustachian tube Air is insufflated into the middle ear daily through the polyethylene tube through which medical preparations can also be injected

The term adhesive otitis we apply at the Otolaryngological University Hospital in Helsinki to an abacterial inflammation of the middle ear and the adjoining pneumatic spaces characterized by prolonged tubal occlusion and formation of tympanic adhesions At the onset there is usually an otosalpingitis with few symptoms, but adhesive otitis may also be preceded by an acute purulent and bacterial otitis media, the infection having been destroyed by the natural defence mechanism of the ear or by antibiotic therapy The tympanic membrane is unperforated in this condition Cases with an open perforation have not been placed under this diagnostic heading In adhesive otitis the drum membrane is retracted and mostly very poorly mobile or immobile, and the pneumatic cell-system is limited and opaque Figs 1 and 2

The development of adhesive otitis is widely attributed to improper treatment of acute otitis media The use of antibiotics without proper drainage, and of air insufflation, easily leads to retention of inflammatory secretions in the middle ear, to their organization with resulting adhesions, and to tubal occlusion In the case of so-called "glue ears", in which subacute otitis media is associated with extremely viscid and mucous secretion, there is evidently a great tendency for adhesive otitis to develop It seems to be due in part to anatomical narrowness of the tube and probably to some other constitutional factor also

Allergy is often mentioned as an etiologic factor in adhesive otitis. In our material we have seen only few patients with an allergic constitution.

Since adhesive otitis resembles mucoviscidosis both histopathologically and as far as certain secretions of glands are concerned, we have investigated the chloride content of the sweat of these patients. In cases of mucoviscidosis the amount of chlorides in sweat is regularly increased, which is typical of this disease. The results of the present investigations yielded normal chloride values, so there is no reason to assume that the adhesive process in the middle ear would be some kind of mucoviscidosis.



Fig 1 Retracted and immobile ear drum



Fig 2 Typical roentgenogram of second stage case of adhesive otitis Pneumatization limited and opaque

The negative pressure in the middle ear, and as its results, disturbed circulation and retention, seem to be the basic causes of the middle ear pathology characteristic of adhesive otitis

Three phases may be distinguished The *early stage* consists in a subacute otosalpingitis characterized by blocking of the tube The tympanic membrane is retracted and — as already stated — the middle ear frequently contains sticky mucous secretion Air insufflation normalizes the tympanal air pressure and results in ' opening ' of the ear, but in the absence of tubal function, the ear is soon blocked again because of the diminishing pressure The pneumatic spaces adjoining the middle ear are also involved A chronic abacterial mastoiditis develops

Granulation tissue and adhesions gradually form in the inflamed spaces, which limits the movements of the tympanic membrane Progress of inflammation leads to the *second stage*, marked by formation of adhesions

In some cases there seems to be a *third stage* inflammation has subsided, the tube is patent and adhesions dominate

The pathological changes in the mucous membrane develop from the acute inflammation present at the early stage to hyperplasia cholesterosis and fibrosis

The middle ear secretion initially low in protein with few cells, becomes mucous during the first few weeks and phagocytizing cells and cholesterol crystals are seen in it The pneumatic cell system of young patients develops poorly because of absent ventilation and of inflammation Reduction of the cell system evidently takes place in a later phase of the illness

The *treatment* of adhesive otitis depends on the stage of disease *At the subacute early stage* particular attention should be given to the elimination, by medical and operative treatment, of the factors maintaining occlusion Cases of sinusitis must be treated and nasopharyngeal adenoid tissue removed by operation and/or radiation Any secretion should be removed and air insufflated into the middle ear If these procedures do not suffice for curing the disease, it is advisable to perform mastoidectomy as the inflammation in the air spaces — even an abacterial one — seems productive of middle ear secretions and maintains inflammation and tubal occlusion Should the tube be narrow, it may be of benefit to inflate air through a mastoidectomy incision with the aid of a drainage tube placed in the aditus of the antrum Air content of the middle ear can thus be ensured The same drain also temporarily takes over from the tube the ventilation of the tympanum Instillation of penicillin–cortisone–alfa–chymotrypsine in our experience helps to clear the inflammation and restore patency of the tube In view of the fact that patients with adhesive otitis seem to have a particular tendency to adhesions we have tried at this early stage and also in general to avoid trauma to the middle ear mucosa Proper treatment at the subacute initial stage usually results in cure In the case of child patients with a particularly narrow eustachian tube it is advisable to go on with air inflations to preclude recurrences which otherwise tend to develop Often it is impossible to avoid stretching of the drum membrane in these cases This does not seem to

affect hearing very much, however What is most important is the prevention of adhesions and tubal blockage

In some cases we have used the polyethylene tubing recommended by Armstrong for drainage and ventilation of the middle ear through an opening in the drum membrane (Fig 3) This tubing has been left in place for several weeks



Fig 3 Polyethylene tubing inserted into the middle ear through an opening in the drum membrane

and kept open by daily aspiration After removal of the tube the opening in the drum membrane has closed rapidly

Once adhesions have developed successful therapy is much more difficult than at the initial stage when restitutio ad integrum is generally possible The changes in the middle ear vary considerably with the degree of intensity of the adhesive process At the beginning of the second stage there is still air filled space in the middle ear and the adhesions are string or sail like The ossicular chain and the tympanic membrane are mobile at least to some extent and the middle ear shows areas where the mucous membrane is well preserved In advanced cases the tympanic membrane may be entirely fixed by adhesions and immobile the middle ear mucosa may be fibrotic or destroyed and the ossicular chain rigid or, in the area of the long process of the incus atrophied or broken off or the stapes may be decalcified and soft The windows may be free or closed by adhesions The changes in the tympanum vary widely from one case to another Even though the air space of the middle ear may be entirely lost remnants of lumen are usually found in the region of the tympanal opening

The aims of the surgical procedures in these cases are separation of the tympanic membrane from the promontory, restoration of the middle ear airspace and of patency of the tube, freeing the window niches and ossicles from adhesions, and reconstruction or mobilization of the ossicular chain As at the early stage, it is also now necessary to treat any sinusitis or mastoiditis that may maintain inflammation and to remove stenosing adenoid tissue blocking the tube It is our experience that patients with adhesive otitis have an extremely great tendency to formation of new adhesions This must be kept in mind in surgical therapy especially and needless traumatizing of the mucosa avoided

The surgical approach in our clinic has been through an endaural or retro auricular incision The latter has been used when performing at the same time a mastoidectomy, which is usually necessary during the second stage The middle ear is opened by freeing the meatal skin and the margin of the tympanic membrane from the bony ear canal Freeing of the tympanic membrane without damage to it often requires chiselling of the inner portion of the bony meatus as the tympanic membrane generally is so much retracted as to rupture easily when the annulus is dissected free Great care is essential in dissecting the tympanic membrane free, ruptures impair the chances of a good end result The ossicular chain and the window niches are freed from adhesions and the tubal opening exposed If there are few adhesions, sectioning may be desisted from experience has shown that mastoidectomy and air insufflation through the aditus into the middle ear often suffice for aeration and restoration of the middle ear mucosa and of tubal function Fig 4

If the tympanic membrane is entirely fixed to the medial tympanal wall, then

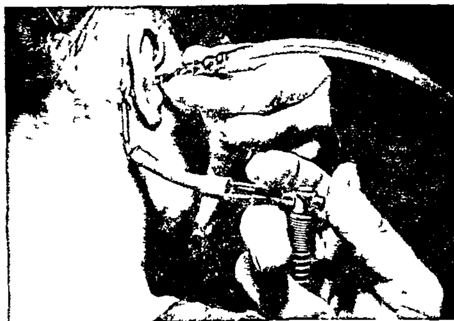


Fig 4 Insufflation of air through a drain (placed in aditus ad antrum) in the mastoidectomy wound

a large portion of the tympanic mucosa is also usually destroyed The drum is flaccid and the ossicular chain rigid atrophic or broken In these cases it may be best to be content initially with restoration of the air space of the middle ear which as such seems to have a curative effect on hearing A 1 5 mm polyethylene tube is introduced into the eustachian tube and pushed out through the nostril on the same side Its aural end is attached with a knot to the operation wound A polyethylene tube with a funnel shaped end is inserted into the middle ear The funnel prevents the tube from slipping out If the tympanic membrane is very thin and flabby or if ruptures have occurred in it, support can be obtained by placing a thin piece of temporal fascia on the inner side of this membrane

During postoperative care it is attempted as far as possible to keep the surgically created middle-ear lumen open by air insufflation (Fig 5) and instillation of saline or penicillin cortisone solution At the same time the patients have received dexamethason tablets which we hope also will prevent the development of adhesions The results are expected to improve gradually with increasing experience

At the terminal stage when inflammatory changes are no longer present and



Fig 5 Insufflation of air with needle and syringe through polyethylene tubing into the middle ear after operative restoration of air filled tympanum

deafness is due to inflammatory adhesions and to fixation of the ossicles, we have mostly used a stapes operation similar to the one employed in otosclerosis At this operation the stapes plate is replaced by temporal fascia and either the crura or a polyethylene tube are utilized for conducting sound from the long process of the incus, or directly from the drum membrane, to the oval window

In two thirds of the patients the disease was bilateral and most of the patients were young people The disease seems to be equally frequent among men and women In the early stage, however, — the majority of the patients being children — boys seem to be more commonly affected than girls In the later stages of the disease female patients predominate In the initial stage the average age of the patients was 10 years, in the second stage, marked by formation of adhesions, average age was 26, and in the terminal stage 41 years

Treatment at the initial stages has usually led to good results, hearing has returned to normal or nearly normal These are not yet cases of adhesive otitis in the proper sense of the term

As a rule hearing was badly impaired in all ears at the adhesive or the terminal stage By means of the operation used by us a considerable improvement has been achieved in many cases Of the ears operated upon during the last two years hearing has improved in ca 80 % to a variable extent according to the degree of serverity of the case The results of therapy areseen in Table I and Figs 6—9 The time of observation varies from almost 1 5 years to two months

Table I *Results of therapy*

Adhesive stage	43 ears
Eustachian tube open	41 ears
Improvement of hearing	35 ears
Improvement of hearing more than 10 db	22 ears
Terminal stage	15 ears
Eustachian tube open	15 ears
Improvement of hearing	11 ears
Improvement of hearing more than 10 db	7 ears

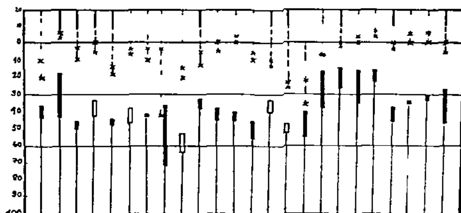


Fig 6 Results of surgery in ears operated in 1962
Black bars show postoperative air conduction improvement Open bars indicate corresponding postoperative loss

a large portion of the tympanic mucosa is also usually destroyed. The drum is flaccid and the ossicular chain rigid, atrophic or broken. In these cases it may be best to be content initially with restoration of the air space of the middle ear, which as such seems to have a curative effect on hearing. A 1.5 mm polyethylene tube is introduced into the eustachian tube and pushed out through the nostril on the same side. Its aural end is attached with a knot to the operation wound. A polyethylene tube with a funnel-shaped end is inserted into the middle ear. The funnel prevents the tube from slipping out. If the tympanic membrane is very thin and flabby, or if ruptures have occurred in it, support can be obtained by placing a thin piece of temporal fascia on the inner side of this membrane.

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At the terminal stage, when inflammatory changes are no longer present and



Fig. 5. Insufflation of air with needle and syringe through polyethylene tubing into the middle ear after operative restoration of air filled tympanum.

great interest the thorough investigations of Ingelstedt, Örtegren and Flisberg published in a recent series of papers from the Lund-clinic Their work will be of invaluable help to us and other investigators in studying the function of the middle ear and the Eustachian tube

In my opinion it is generally possible by adequate treatment to avoid the *formation of tympanic adhesions which may otherwise arise* in cases of chronic tympanosalpingitis if the anatomical conditions are unfavourable and constitutional factors contribute But even cases where an adhesive otitis has already developed it still is often possible to restore an air filled middle ear cavity, function of the Eustachian tube, and a normal or at least satisfactory conduction

CONCLUSIONS

Proper treatment of cases of acute otitis and subacute otosalpingitis is essential with a view to avoiding adhesive otitis and the resulting deafness This is the best prophylaxis of adhesive otitis Once adhesions have developed it is still possible to improve hearing by restoring the tubal function, an air filled middle ear, and a mobile ossicular chain Treatment of adhesive otitis at the terminal stage aims at overcoming the obstacles in sound conduction due to the rigidity of the ossicular chain or to the obliterated fenestrae

ACKNOWLEDGEMENT

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CHRONIC ADHESIVE OTITIS

ANALYSIS OF SOME PREDISPOSING FACTORS

By

Sven Ingelstedt

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Abstract

Several predisposing factors are determined by different new methods applied to normal and diseased ears The data obtained provide further information on the problem of prophylaxis

The following factors have been studied 1) ear drum mobility and elasticity, 2) the pneumatic ear system 3) the Eustachian tube function

In chronic adhesive otitis, as in all diseases, prevention is better than cure Unfortunately, however, it is not always possible to detect the condition early enough for adequate prophylaxis Therefore I thought it worth while to investigate some phenomena which have apparently hitherto escaped attention and which, if they happen to occur in a certain combination, may favour the development of chronic ear diseases

Fig 1 gives some of the factors we have been studying at the ENT department

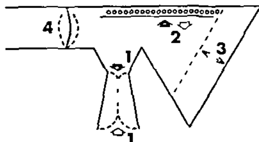


Fig 1 Factors involved in the ventilation of the air filled ear space 1 Tubal ventilation 2 Gas diffusion 3 Air space 4 Mobility of drum

in Lund for some years, and the results obtained have recently been published in supplementum 182 of Acta Otolaryng The factors I intend to discuss here today are the function of the Eustachian tube as a pressure regulator and ventilator of the tympanic cavity, the transport of gas between the air of the ear space and the blood vessels of the mucosal lining, the volume of the air-filled ear space and finally the elasticity and mobility of the eardrum

Assessment of these functions enables a much clearer understanding and evaluation of the injurious effect any disorder of the normal interplay of these factors will have on the function of the middle ear

Function of Eustachian tube

The partial pressure of oxygen of the air in the tympanic cavity is normally higher than the oxygen tension of the blood in the vessels of the mucosal lining Normally, then, oxygen is continuously diffusing from the enclosed air to the blood, which results in a lowering of the pressure within the middle ear The air pressure on both sides of the tympanic membrane *i e* the intratympanic on the *inside* and the extra tympanic, or barometric, on the outside is equalized by the acts of swallowing which open the tube and thereby allow air from the rhinopharynx to enter the tympanic cavity In other words ventilation of the middle ear, *i e* replacement of air used up or resorbed by the vessels of the mucosa, lining the cavity, is brought about *by suction* of air into the cavity

We also know that if the Eustachian tube is suddenly occluded, the intra tympanic pressure will within one hour be about 10—20 mm Hg below the extratympanic

These observations provide a clue as to how tubal function should be studied In other words the design of the test should mimic the physiological mechanisms as closely as possible

The question that then unsought arises is How should such a test be designed to satisfy this requirement? We use the following arrangement Via an existing perforation or an incision in the drum a closed eletric manometer system is connected air tight to the tympanic cavity, by means of a cuff inflated with glycerine and placed in the bony part of the external auditory canal The examiner then lowers the pressure in the closed system consisting of the ear and the manometer The negative pressure within the system will remain constant at the level set until the Eustachian tube has opened and offered entry of atmo spheric air into the ear The patient is then instructed to swallow, and the con sequent degree of equalization of the pressure provides a measure of tubal func tion With knowledge of the volume of air in the manometer system plus the closed ear space, and direct recording of the change in the pressure prevailing in the cavity during each act of swallowing, tubal ventilation can be calculated in units of volume (mm^3)

Fig 2 illustrates a series of such tests on a normal volunteer after incision of the drum The lower curve (open circles) shows the amounts of air in mm^3 sucked into the ear at each act of swallowing during varying degrees of intra aural negative pressure It is clear from the diagram that the amount of gas sucked into the tympanic cavity during an act of swallowing decreases with increasing ne gative pressure in the closed space of the ear We call the mechanism responsible for this phenomenon *occlusion by suction* because the aural portion of the tube is most probably narrowed by direct suction produced by the lower pressure within the tympanic cavity The upper curve (filled circles) in Fig 2 was also traced after production of various degrees of negative pressure in the tympanic cavity but now a constant pressure of −5 mm Hg was applied to the rhinopharynx during all acts of swallowing This causes a radical change of the ventilation of the middle ear If we now select 2 points on the two curves which

in spite of different experimental conditions represent *the same absolute difference in pressure* between the middle ear and the rhinopharynx during an act of swallowing e g the 2 points joined by the continuous bold line in the figure, the

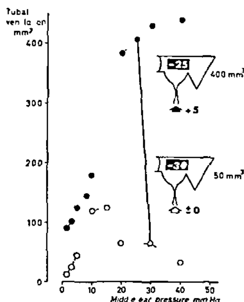


Fig 2 Comparison between effect of varying degrees of negative intratympanic pressure with (filled circles) and without (hollow circles) application of positive pressure in rhinopharynx on tubal ventilation

absolute difference in pressure at these two points is 30 mm Hg Despite this, tubal ventilation of the middle ear, as judged by volume is 8 times greater during swallowing when application of the negative pressure (—25 mm Hg) within the ear *is accompanied by application of a slight positive pressure* (+5 mm Hg) in the rhinopharynx, *i e* inflation than when the ear is ventilated by aspiration only (—30 mm Hg) It is true that the difference between the results in these two experiments is not always so pronounced as in the normal subject illustrated but the tendency is always clearly the same In the presence of a common cold, on the other hand the difference in the volume of tubal ventilation after aspiration alone and after aspiration + inflation, is usually more marked than that shown in Fig 2, a point which I will revert to later

We think that these observations should be borne in mind in the investigation of the rôle played by the Eustachian tube in the diseases of the middle ear For, as we all know, formerly primary inflammatory changes of the mucosa lining the tube were believed to play an essential role in the development of otitis media, *i e* the ex vacuo theory Later, however, Zollner, for example, in his excellent monograph on the Eustachian tube, is inclined to belittle the rôle played by the tube in the causation and course of secretory otitis media Zollner appears to have based his conclusion on the observation that air can readily pass through the tube to the middle ear during the act of swallowing when positive pressure is applied in the rhinopharynx But I doubt whether this experiment

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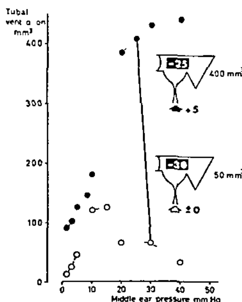


Fig 2 Comparison between effect of varying degrees of negative intratympanic pressure with (filled circles) and without (hollow circles) application of positive pressure in rhinopharynx on tubal ventilation

absolute difference in pressure at these two points is 30 mm Hg Despite this, tubal ventilation of the middle ear, as judged by volume, is 8 times greater during swallowing when application of the negative pressure (—25 mm Hg) within the ear is accompanied by application of a slight positive pressure (+5 mm Hg) in the rhinopharynx, *i e* inflation, than when the ear is ventilated by aspiration only (—30 mm Hg) It is true that the difference between the results in these two experiments is not always so pronounced as in the normal subject illustrated but the tendency is always clearly the same In the presence of a common cold, on the other hand, the difference in the volume of tubal ventilation after aspiration alone and after aspiration + inflation, is usually more marked than that shown in Fig 2, a point which I will revert to later

We think that these observations should be borne in mind in the investigation of the rôle played by the Eustachian tube in the diseases of the middle ear For, as we all know, formerly primary inflammatory changes of the mucosa lining the tube were believed to play an essential rôle in the development of otitis media, *i e* the ex vacuo theory Later, however, Zollner, for example, in his excellent monograph on the Eustachian tube, is inclined to belittle the rôle played by the tube in the causation and course of secretory otitis media Zollner appears to have based his conclusion on the observation that air can readily pass through the tube to the middle ear during the act of swallowing when positive pressure is applied in the rhinopharynx But I doubt whether this experiment

warrants such a conclusion, because the passage of air through the tube by application of positive pressure in the rhinopharynx cannot, and should not, be interpreted as a sign of normal tubal function, because normally the ear sucks in air through the tube during the act of swallowing solely as a consequence of the negative pressure prevailing within the middle ear

Considerations on absorption of gases by blood vessels of mucosa lining air-filled ear space

The rate of gaseous exchange between these two media is governed by the following well known factors

1 Any substance will always move from a region of higher concentration to one of lower concentration according to the fundamental laws of diffusion Consequently, the higher the partial pressure of a gas in the closed chamber of the ear is than that of the blood and the tissues enclosing the gas, the greater the amount of gas that will diffuse out of the ear space
2 The more soluble the gas is in the membranes separating the gas phase from the blood phase, the more readily the gas will diffuse Therefore the diffusing capacity of CO_2, for example, is much greater than that of O_2
3 Surface area for diffusion and the number of patent blood perfusing capillaries in the membranes
4 Distance for diffusion *Diffusion is impaired by mucosal oedema*

Investigation of the significance of these factors in the function of pulmonary alveoli is difficult enough but elucidation of the rôle they play in the human ear *is much more* complicated and difficult The *investigations* hitherto published on the composition of the gases in the tympanic cavity under different experimental conditions have been done in the presence of a number of the above mentioned variables unknown to those examiners Moreover no satisfactory methods have ever been available for obtaining a representative sample of the gas in the middle ear We have for some time focused attention on this field but we have not yet succeeded in devising a method satisfactory from both a methodological and physiological point of view, to warrant publication of our preliminary results We are, however, convinced that these problems must be solved before we can expect a better understanding and wider knowledge of the physiology and pathophysiology of the mucosa lining the air filled ear spaces

In order to illustrate the mechanisms of the diffusion of gases, I have therefore been obliged in Fig 3 to draw an analogy between the ear and a subcutaneous gas pocket the latter having been the subject of intense investigation Several studies on the behaviour of the subcutaneous experimental gas pocket containing air (particularly *Rahn* and co workers) show that already within some hours after injection of ordinary air, the gas tensions in the pocket tend to approach those of the gases in the surrounding venous blood Several investigations of the composition of the gases in human pneumothorax pneumoperitoneum and subcutaneous gas pockets have been published, and they

have almost all shown that, irrespective of the original composition of the gas injected, the fractions of O_2, CO_2 and N_2 in the pockets will sooner or later become constant The values then obtained are usually of the same order as those obtained from the venous blood draining the pocket tissues

But a subcutaneous compressible gas pocket (upper sketch in Fig 3) is com-

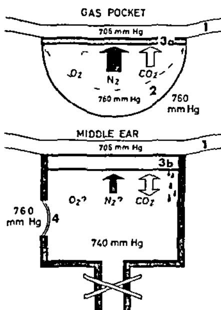


Fig 3 Comparison between diffusion of gases in a subcutaneous gas pocket and in the middle ear space 1 Sum of venous blood gas tensions 2 Elasticity of gas pocket wall 3 a Normal membrane between blood and gas phases b Oedematous membrane between blood and gas phases 4 Tympanic membrane

pletely absorbed for, owing to the elasticity of the pocket walls the total pressure in the gas depot remains constant in the neighbourhood at atmospheric pressure, while the total sum of the gas tensions in the venous blood (1) surrounding the pocket is always lower than the atmospheric pressure But the closed air-filled ear spaces cannot be compared to a gas pocket with yieldable or elastic walls, for the ear consists of a bony cavity with largely unyieldable walls When the tube is closed, the concentration of oxygen in the enclosed air is initially higher than that in the venous blood The oxygen is absorbed with the result that the intratympanic air pressure will gradually become lower than the extratympanic, but long before the partial pressure of the oxygen in the gaseous phase has time to reach the tension in the venous blood, the relatively low pressure will have produced oedema of the mucosa (3 b) lining the ear spaces and transudation will gradually occur This oedema impairs the transport of gases between the ear spaces and the blood It is probable that the oedema *per se* does not obstruct the passage of CO_2 from the blood to the closed space There is, however, good reason to suppose that the partial pressure of oxygen, in the presence of oedema of the mucosa, often is lowered below the oxygen tension level of the venous blood draining the mucosa,

and this lowering is then caused by oxygen consumption by the surface epithelium of the mucosa, since the oxygen is now directly taken from the gas enclosed in the ear spaces This consumption of gas will surely be greater if microorganisms enter the ear cavity, but the oedema of the mucosa now seriously obstructs the diffusion of oxygen from the blood into the ear spaces In acute inflammation with intense hyperaemia of the mucosa the situation will not seriously interfere with diffusion from the blood but if the otitis is 'abacterial' or chronic due to low-virulent microorganisms, the air enclosed will surely be relatively poor in oxygen and relatively rich in carbon dioxide A question that then presents itself is How do such environments affect any microorganisms present? We know that some of them are facultatively anaerobic, e g pneumococci But that is about all we do know Chronic perforation of the drum may therefore often be regarded as the only way for nature to cure a chronic inflammatory process of the middle ear It would therefore appear that in some of these cases myringoplasty will not improve but worsen the state of the middle ear and thereby invite recurrence of the disease This will also help to explain why the operation will not always produce the desired effect

Tubal function in common cold

We have studied a number of persons who shortly after they had caught a common cold with acute catarrhal symptoms of the nose, throat and rhinopharynx but before any ear symptoms have had time to develop and before otoscopy had revealed any signs of a pathologic condition of the drum In the examination of these patients an incision was made in the drum and the closed manometer system I described a while ago was connected airtight to the closed ear spaces and the pressure in the closed ear + manometer system was lowered The patient was then instructed to swallow, and the resulting decrease, if any, in the middle ear pressure was recorded In many of these patients swallowing could not eliminate such a small intra aural pressure as —5 mm Hg, — the tube was locked In healthy volunteers, on the other hand, such locking did not occur until the intratympanic pressure had been reduced to 30—50 mm Hg or more below the extratympanic This complete occlusion of the tubal lumen by the suction produced by such a slight negative pressure in the ear in patients with a cold was probably facilitated by a certain degree of mucosal catarrh in the actual tube But this locking was always readily interrupted on application of even a very slight positive pressure to the rhinopharynx during the act of swallowing This means that the mucosa of the upper isthmus which was interlocked by the suction produced by the negative pressure in the middle ear was unlocked by application of pressure in the rhinopharynx

An interesting observation was the reaction of the negative pressure in the tympanic cavity to the act of swallowing in patients with a cold and locked Eustachian tubes This phenomenon is illustrated in Fig 4 and shows that every act of swallowing was accompanied by accentuation of the negative pressure in the middle ear These accentuated negative pressure spikes in the case illustrated

in the figure correspond to a pressure of 1 mm Hg after which the negative pressure after swallowing returns to its original level of —5 mm Hg, which means that no air has passed through the tube from the rhinopharynx to the ear This phenomenon must imply that the volume of air in the closed chamber continues to be enclosed during the act of swallowing at the same time as the volume of the chamber increases slightly In the present case this increase in volume was calculated to be 13 mm³ for every act of swallowing This accentuation of the negative pressure prevailing in the ear must lock the tube still tighter In other words, the muscles normally opening the tube during swallowing have the opposite effect, in that they will close the tube still tighter

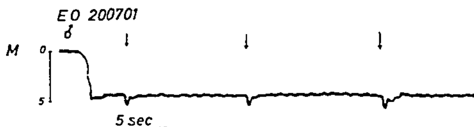


Fig 4 Intratympanic air pressure during the locking period Arrows denote accentuation of negative pressure during act of swallowing

What effect have changes in the volume of the air filled ear spaces and in the elasticity and mobility of the drum on tubal function in common cold?

The possibility of the ear to cushion and counteract the above-mentioned accentuation of the negative pressure is dependent, of course, on the volume of the air filled ear space and on the prevailing mobility of the ear drum inwards To illustrate the effect of these variables on the ear as a system we calculated the effect of a 10 mm³ increase of the volume of closed ear spaces of 9, 3 and 1 ml respectively Since we had devised methods for assessing the rôle of the normal drum as a regulator of the pressure in the middle ear, we applied the results obtained by these methods to ascertain (a) how much the negative pressure spikes caused by the increase in volume of an enclosed chamber could be reduced by the presence of a normal drum in the system (the resulting accentuation to the right in Fig 5 is marked by dotted line) and (b) how large the corresponding pressure spikes will be in the presence of an immovable drum in the system (resulting accentuation marked by continuous line to the right in Fig 5) In all three ear systems sketched to the left in Fig 5, an initial constant negative pressure of —3 mm Hg is assumed Owing to this negative pressure the tubal mucosa of the isthmus' portion nearest the ear is sucked into the lumen of the bony portion of the tube and marked by continuous lines in all the drawings in Fig 5 During the act of swallowing (dotted outline) this mucosa drawn into the bony tube is somewhat withdrawn by the activity of the opening muscles of the tube In all 3 examples this withdrawal increases the closed volume of the air filled space by

and this lowering is then caused by oxygen consumption by the surface epithelium of the mucosa, since the oxygen is now directly taken from the gas enclosed in the ear spaces This consumption of gas will surely be greater if microorganisms enter the ear cavity, but the oedema of the mucosa now seriously obstructs the diffusion of oxygen from the blood into the ear spaces In acute inflammation with intense hyperaemia of the mucosa the situation will not seriously interfere with diffusion from the blood but if the otitis is "abacterial" or chronic due to low virulent microorganisms, the air enclosed will surely be relatively poor in oxygen and relatively rich in carbon dioxide A question that then presents itself is How do such environments affect any microorganisms present? We know that some of them are facultatively anaerobic, *e g* pneumococci But that is about all we do know Chronic perforation of the drum may therefore often be regarded as the only way for nature to cure a chronic inflammatory process of the middle ear It would therefore appear that in some of these cases myringoplasty will not improve but worsen the state of the middle ear and thereby invite recurrence of the disease This will also help to explain why the operation will not always produce the desired effect

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It is thus clear that in a person with small air-filled ear spaces and decreased mobility and elasticity of the drum, even a slight common cold will be enough to impair or prevent opening of the tube by the act of swallowing alone It is also clear that the rôle of the normal drum as a damper of the negative pressure spikes occurring during swallowing will be greater and greater the smaller the volume of the air-filled system

Another factor favouring diseases of ears with small air spaces is worth mentioning It must reasonably be supposed that the mucosa lining the normal middle ear cavity, especially the drum, is much more richly vascularized than the mucosa of the cell system This implies that the major part of the diffusion of oxygen from the air in the ear space to the blood must always occur via the middle ear mucosa, irrespective of the size of the cell system

In the light of all these factors taken together we do not think it remarkable that the tube is more liable to be locked in an ear with a small air space and impaired elasticity and mobility of the drum in association with a common cold, and thereby pave the way for microorganisms to invade the middle ear

A few remarks on therapy

We recommend a revival of over-pressure ventilation via the rhinopharynx of the middle ear It is the only possibility to unlock the tube, especially if the ear space is small and if the elasticity of the drum is impaired Once the tube is locked and left untreated mucosal oedema will very soon occur, probably within an hour, because of the increasing negative pressure, and provide excellent soil for complicating infection of the middle ear The risk of introducing microorganisms via the tube in association with positive pressure ventilation and consequent otitis is probably much less

Attempts should be made with all possible means to preserve the normal elasticity of the drum Attempts should also be made to control any tendency to inflammatory obliteration of the air cell system

From a theoretical point of view it would also appear justified surgically to create a cell system in patients whose ears have no such system, provided that free communication can be maintained between the cell system and the tympanic cavity

Finally, some of the cases of chronic secretory otitis may be treated by a procedure differing from the conventional methods (Fig 6) before the disease has had time to produce serious damage to the middle ear After roentgen examination of the ear with an indicator placed over the mastoid process, the cell system may be punctured and the ear irrigated by intra aural drip with physiological saline preferably containing some enzyme or steroid Such irrigation removes mucinous fluid from the ear space through the tube more effectively than what is possible by simple incision of the drum Moreover, myringotomy may in some cases pave the way for secondary infection of the middle ear, which probably offers favourable environments for growth from the very beginning Used with discretion, irrigation of the mastoid air cells and of the middle ear cavity involves

of the ear–manometer system, calculated according to Boyle's law, delta-V, the amount of air to be calculated (here added to volume V) The initial pressure (P) is known and the change in pressure (delta-P) can be recorded

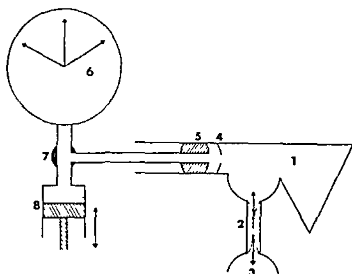
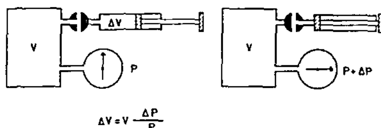


Fig 1 Principle of aspiration' method 1 Air filled ear space 2 Eustachian tube 3 Rhinopharynx 4 Ear drum 5 Rubber cuff 6 Manometer 7 3 way stopcock 8 Syringe



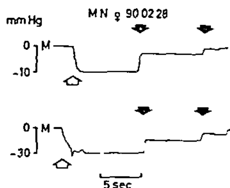
$$\Delta V = V \frac{\Delta P}{P}$$

Fig 2 Principle of volume determination of air passing the Eustachian tube

RESULTS

Fig 3 gives the recordings for a normal person studied by aspiration method At the times indicated by the hollow arrows a pressure of —10 mm Hg (upper curve) and of —30 mm Hg (lower curve) was produced in the ear The subject was instructed to swallow — indicated by filled arrows — and the pressure in the middle ear stepwise changed towards that of the atmosphere every time the subject swallowed, *i e* when air passed through the tube

Fig 4 refers to a patient with chronic otitis The purpose of the examination was to decide whether myringoplasty was indicated The upper curve shows how a positive pressure of 30 mm Hg is produced in the ear and how it disappears stepwise during swallowing — filled arrows The lower curve represents a negative pressure of 30 mm Hg in the middle ear, which also, as seen



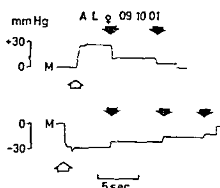


Fig 3 Recordings in normal volunteer M = pressure change recordings in the closed ear space Hollow arrow = application of negative pressure in manometer-ear system Filled arrow = "open nose' deglutition

Fig 4 Recordings in case of chronic otitis Shaded arrow = application of positive pressure in manometer ear system Hollow arrow = application of negative pressure in manometer ear system Filled arrow = open nose" deglutition

disappears during swallowing (filled arrows) Pressure ranges studied in the middle ear were ± 5, 10, 20, 30 mm Hg

With the use of the method described above it is possible to calculate the volumes of air which pass into or out the Eustachian tube during the act of swallowing in association with negative or positive pressure in the middle ear

The volumes for the patient in Fig 4 are given in Fig 5 The black curve represents the volumes passing in through the tube during the act of swallowing after production of different negative pressures in the middle ear The interrupted curve represents the amount of air escaping from the cavity and passing

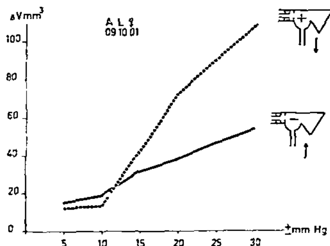


Fig 5 Curve illustrating relationship between middle ear pressure and tubal air passage

out through the tube when the patient swallowed with pre-existing positive pressure in the middle ear

The differences in volumes in these two experiments were considerable, the amount of air passing out of the ear when the pressure in the middle ear was positive being larger than that passing into it when the corresponding pressure was negative This illustrates a well known tubal mechanism

Fig 6 gives the results of an examination of a patient who had a common cold for one day but had no ear symptoms, and the drums were normal

Upper curve — A positive pressure of about 5 mm Hg was applied to the

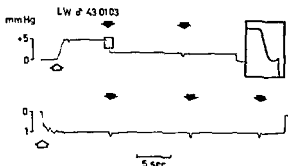


Fig 6 A case of common cold illustrating the locking phenomenon by negative pressure spikes during open nose deglutitions Shaded arrow = application of positive pressure in manometer ear system Hollow arrow = application of negative pressure in manometer-ear system Filled arrow = open nose deglutition

middle ear (shaded arrow) During swallowing (filled arrows) the tube initially tended to become locked (negative pressure spike) but this tendency was overcome and the difference in pressure between the middle ear and atmosphere decreased when air passed through the tube (shape of curve given in larger scale to the right of the curve recorded) During the second act of swallowing the tube did not open in its entirety, the recording showing only a spike

Lower curve — A negative pressure of 1 mm Hg was applied to the middle ear No air was sucked into the ear via the tube during swallowing The tube was locked Negative pressure spikes were recorded synchronously with every act of swallowing These spikes reflected unsuccessful attempts of the tube to open

This thus shows that in a common cold the Eustachian tube is locked by even a slight negative pressure within the middle ear and that a positive pressure in the middle ear can only with difficulty open the tube during swallowing

In both cases negative pressure spikes are recorded during swallowing owing to an increase of the enclosed volume in the manometer–ear system The increase in volume is due to a certain degree of opening of the tube in its upper aural part by muscular action during swallowing while the rest of the lumen of the isthmus is still occluded

Fig 7 shows results of preoperative examination of tubal function in a case in which myringoplastic operation was contemplated

The two upper curves show how negative middle ear pressures of —5 and —10 mm Hg cannot be equalized by swallowing alone (filled arrows) When

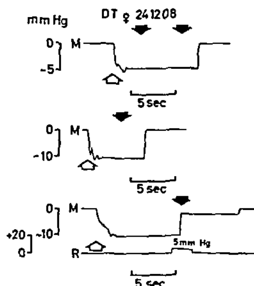


Fig 7 Recordings in a case of chronic otitis illustrating the difference between aspiration and inflation + aspiration M = pressure change recordings in the closed ear space R = rhinopharyngeal pressure changes Hollow arrow = application of negative pressure in manometer ear system Filled arrow = open nose deglutition

however, a negative pressure of 10 mm Hg was applied to the middle ear and a positive pressure of 5 mm Hg to the rhinopharynx, the tube opened during swallowing The absolute difference in pressure between the epipharynx and the middle ear was then the same during aspiration alone (—5 mm Hg) as during combined inflation (+5 mm Hg) + aspiration (—10 mm Hg) Only with the aid of inflation via the rhinopharynx then could air pass into the middle ear, aspiration alone being unable to open the tube Examined by conventional methods then, tubal function in this case would have been regarded as normal

The method described requires special equipment for measuring and recording the pressures In the present investigation the pressure was measured with Elema Schonanders standard electromanometers (EMT 490 A and EMT 490 B) and recorded on a mingograph Such equipment is necessary for research work and analysis of the variation of pressure in the ear and rhinopharynx *i e* determinations necessary for adequate quantitative determination of tubal ventilation

For routine clinical use, however, a simpler apparatus of the type described below may be used with advantage

Simplified technique for examination of tubal function by controlled ear aspiration of air

A simplified method for assessing tubal ventilation by the principle of moving droplet in a pipette earlier used by Politzer in the middle of the last century is devised The novelty of the present method is the use of a simple suction fan

for producing negative pressure in the ear (Fig 8) As before, the auditory duct is connected with a cuff to the bony parts of the auditory canal and a graded pipette is connected to the ear system The pipette contains a drop of mercury, which rises or falls according to the change in pressure in the closed system By

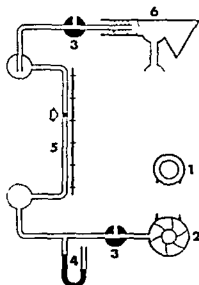


Fig 8 Apparatus for simple clinical estimation of tubal ventilation 1 Autotransformer 2 Fan 3 3 way stopcock 4 Manometer 5 Volumeter with index drop at arrow 6 Ear

means of the fan the desired negative pressure can be produced in the pipette ear system Owing to the inertio of the drop of mercury the pressure above the drop is 1 mm Hg higher than that below with a negative pressure of 10 mm Hg at the manometer

Fig 9 shows the actual pipette with the drop of mercury enclosed and its connections to the ear and fan

This simple apparatus makes an approximate and relatively reliable assessment of tubal function possible

At Lund tubal function is examined in the following way

1 Tubal function test according to aspiration method supplemented with inflation test (The ear must be dry The patient must not have a cold) The test should be done on at least 2 occasions

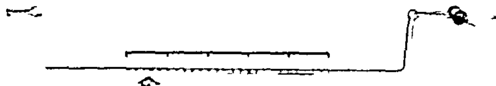


Fig 9 Volumeter Arrow indicates index drop of mercury

2 If function is impaired search for the obstruction
   a) *fluid* blow the ear and Eustachian tube clear e g by the meth
   Politzer
   b) *swollen mucosa* if reduction of swelling gives improvement, func
   mucosal stenosis may be assumed
   c) *organic stenosis* reduction of swelling produces no improvement
   patient should be referred for roentgen examination of the tube (if i
   sary, cineradiography)

SUMMARY

A method is described which is based on examination of the possibilit
the ear to equalize produced positive or negative pressure in the middl
Tubal ventilation can be judged both qualitatively and quantitatively with
zation of fundamental physical laws

The method appears to be an important supplement to conventional infl
methods

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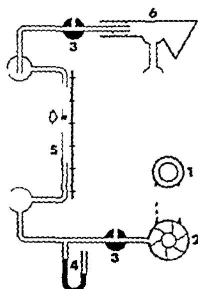


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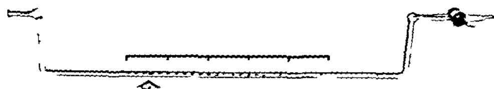


Fig 9 Volumeter Arrow indicates index drop of mercury

Table I *The investigation comprises 121 children of which 74 boys and 47 girls Distribution of age*

7 year	12 pt	boys 7	girls 5
8 »	12 »	» 7	» 5
9 »	17 »	» 11	» 6
10 »	20 »	» 12	» 8
11 »	15 »	» 9	» 6
12 »	8 »	» 6	» 2
13 »	21 »	» 9	» 12
14 »	16 »	» 13	» 3
Total	121 pt.	boys 74	girls 47

brane Later on van Dishoeck has brought the pneumophone into the tubal diagnostics (18)

In his fundamental work concerning clinical investigations of the acoustic impedance of the middle ear, Metz has proved that alterations of the middle ear pressure result in corresponding differences of the impedance, and he suggested that this function could be used as indication of the air passage through the Eustachian tube (19) Thomsen has combined the apparatus of Zollner with the acoustic measuring bridge and thus used the alterations of impedance through the middle ear as indication of variation in middle ear pressure (20 21) In 1957 Thomsen published an investigation concerning the tubal function in 100 normal persons (22) The following factors were studied

1 The minimal overpressure in nasopharynx giving tubal passage during swallowing,
2 The pressure/absorption curve from the middle ear indicating the valve function from ear drum to rhinopharynx,
3 Number of deglutitory movements necessary for levellating the overpressure in the middle ear,
4 The Toynbee test

In 1960 Terkildsen and Scott Nielsen have continued the development of the acoustic measuring bridge (23), and in this investigation the impedance meter of Terkildsen and Scott Nielsen has been used

Own Investigation

The series comprises 121 children between 7 and 14 years of age The distribution of age is seen from Table I The hearing classifies the cleft palate children into three groups 1 Children with normal hearing and slight hearing losses until 20 db 2 Children with hearing losses of more than 20 db at at least two frequences 3 Children with hearing losses of more than 30 db at at least two frequences

The distribution in groups 2 and 3 is seen in Fig 1, and it will be seen that the frequency of hearing loss is increasing during the first 2—3 years and later

STUDIES ON THE HEARING AND THE TUBAL FUNCTION IN A SERIES OF CHILDREN WITH CLEFT PALATES

(Preliminary report)

By

J Wittenborg Paulsen

From the State Institute of Speech Disorde s, Copenhagen (Head E Forchhammer, Oto-logist K Faaborg Andersen) and the Ear, Nose and Throat Department of the Sundby Hospital, Copenhagen (Head Otto Metz)

Abstract

The study involves hearing data obtained from pure tone air conduction threshold tests of 121 children with cleft palates 60 children show hearing losses bigger than 20 db at two frequences 71 subjects show abnormal tympanic membranes the subject classification includes tubal function tests with employment of impedance measurements of the middle ear

The treatment of children born with cleft palates is in Denmark centralised in a teamwork comprising surgical management, correction of speech disorders, prosthetic management and dental correction On the contrary the audiological examination and treatment depend on the schools and audiological clinics

To get an impression of the handicap of these children a correlation is made between hearing and other factors important for the hearing, first and foremost the tubal function

Much literature has been published concerning the hearing loss in children born with cleft palates, but the various series are not easily comparable because of the different criteria for hearing impairment The ciphers are fluctuating between 40 % and 50 % with a hearing loss of 20 db at at least two frequences (1 2 3 4 5 6 7 8 9 10) In most cases the hypacusis has been moderate and almost always showing a conductive hearing loss (7)

The increased frequency of hearing loss in cleft palate children has been explained from many different factors, of which the following show some statistical significance, 1 relapsing otitis media cases (1 3 8), 2 hyperplasia of the adenoids (2 8 11 12 13), 3 stenosis of the Eustachian tube (4 5 8), 4 deformities of the nasal cavities (12), and 5 dysfunction of the tensor veli palatini muscle (1 14 15)

As far as I know no publication concerning the tubal functions in cleft palate patients have ever been published This investigation, however, is based on methods previously applied on patients with a normal palate function

The investigations of Zollner in 1936 and 1942 (16 17) showed that the air passage through the Eustachian tube could only be performed during swallowing agaist a certain minimal pressure applied in the nasopharynx The indication for tubal passage was the outward movement of the tympanic mem

Table II.

	Number of pts	Boys	Girls	Ear pathology	Hearing loss > 20 db
				Number	Number
1. Bilateral cleft lip and palate	18	11	7	11	13
2 Unilateral cleft lip and palate	52	36	16	33	24
3. Cleft hard and soft palates	19	11	8	11	12
4 Cleft soft palate	28	14	14	13	8
5 Submucous cleft palate	4	2	2	3	3
Total	121	74	47	71	60

Table III.

	Pathol	Cong.	*Perf*	Cicatr	*Retract*	*Adhaes*	*Op* cav	*Hearing loss* >10 db	>20 db	>30 db
1. Bilateral cleft lip and palate	19	0	5	6	7	1	0	29	16	4
2 Unilateral cleft lip and palate	52	1	7	19	24	1	1	79	40	13
3 Cleft hard and soft palates	22	2	8	8	3	1	0	32	22	10
4 Cleft soft palate	16	0	4	8	4	0	0	36	10	1
5 Submucous cleft palate	6	0	1	2	3	0	0	7	6	3
Total	115 (48 %)	3 (1 %)	25 (10 %)	43 (18 %)	41 (17 %)	3 (1 %)	1 (0.4%)	183 (76 %)	94 (39 %)	31 (13 %)

on decreasing during the 13th and 14th year of age In the total classification 60 children, i e 50 % show a hearing loss of more than 20 db at two frequences, and 25 children, i e 21 %, show a hearing loss of more than 30 db

In Table II is seen the relationship of ear pathology and hearing loss to classi-

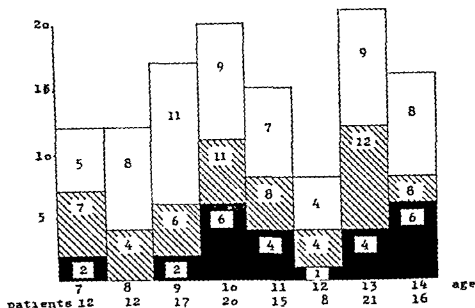
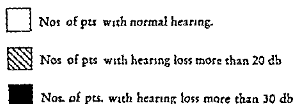


Fig 1



fication of cleft palates into the five classical groups The frequency of the pathological abnormities *in the middle ear and the hearing impairment* is considerably less pronounced in children with cleft entirely in the soft palate It should be pointed out that this classification is established in spite of the fact that all children but two have had their cleft palate closed surgically within the first two years of life

Table III shows the nature of the ear abnormities found It will be seen that the catarrhal otitis media with retraction and later on adhesion of the tympanic membrane is most frequent in groups 1, 2, and 5, whereas the occurrence of perforations is more pronounced in groups 3 In group 4 less pathological changes and better hearing are observed

Scar changes and retractions of the tympanic membrane are the abnormities most frequently seen in cleft palate children

The result of the surgical management and its correlation to hearing appears from Table IV Here the series is divided into three groups 1 patients with prosthetical management 2 patients with surgical management and insufficience of

Fig 2 Correlation between ear pathology, hearing loss and prosthesis contra surgical management

	A		B		C	
	7 pat ears	7 hear loss	23 pat ears	19 hear loss	38 pat ears	34 hear loss.
Patients	11		37		73	

A Prostesis management
B Surgical management with insuff of velophar closure
C. Surgical management with suff of velophar closure

	A		B		C	
	12 pat ears	13 hear loss	37 pat ears	28 hear loss	62 pat ears	49 hear. loss.
Ears	22		74		146	

Fig 3 Correlation between ear pathology, hearing loss and width of cleft palate

	A		B		C	
	6 pat ears	4 hear loss	37 pat ears	24 hear loss.	25 pat ears	27 hear loss
Patients	12		63		42	

A Width of cleft palate 0— 8 mm
B Width of cleft palate 9—12 mm
C. Width of cleft palate more than 12 mm

	A		B		C	
	10 pat ears	6 hear. loss	57 pat ears	41 hear. loss.	41 pat ears	40 hear loss
Ears	24		126		84	

Table IV. *Ear pathology*

	Prosthesis management		Surgical management			
			Insuff of velar-phar closure		Suff of velar-phar closure	
	pts	ears	pts	ears	pts	ears
1 Bilateral						
Cleft lip and palate	3		9		6	
Ear pathology	2	3	5	9	4	6
Hearing loss 20 db	2	4	4	5	4	6
2. Unilateral						
Cleft lip and palate	2		23		27	
Ear pathology	0	0	14	22	16	27
Hearing loss 20 db	0	0	12	18	13	18
3 Cleft, hard and soft palate	3		2		14	
Ear pathology	3	6	2	4	6	12
Hearing loss 20 db	3	6	2	4	7	12
4 Cleft soft palate	1		3		24	
Ear pathology	1	1	2	2	10	13
Hearing loss 20 db	1	1	1	1	8	9
5 Submucous cleft palate	2		0		2	
Ear pathology	1	2			2	4
Hearing loss 20 db	1	2			2	4

the velopharyngeal closure and 3 patients with surgical management and sufficient velopharyngeal closure

The division is made more evident by expressing the result in columns referring to number of patients and number of ears

From Fig 2 it will be seen that prosthetical management makes the biggest amount of ear complications and that the smallest incidence of abnormities is seen in the last group of patients with sufficient velopharyngeal closure

Correlation between width of cleft palate at the time of surgical management and the ear pathology is illustrated in Fig 3 The pathological findings in the middle ear and the hearing are to a certain extent dependent on the width of the cleft palate and it can be concluded that the wider the cleft palate, the bigger the possibilities of hearing complications

Tubal Function Tests in Children with Cleft Palates

This series comprises partly a normal series of children, totally 13 between 7 and 14 years of age with normal hearing, normal otoscopic findings and no former ear complications, and partly a series of 31 cleft palate children extracted from the above-mentioned series The number of ears in the first group are 23 and in the second group 61

Using an apparatus which is able to graduate an overpressure in the nasopharynx during a deglutitory movement you have measured the minimum over pressure in nasopharynx giving air passage through the Eustachian tube while swallowing a little water The indication for air passage is seen from the fact

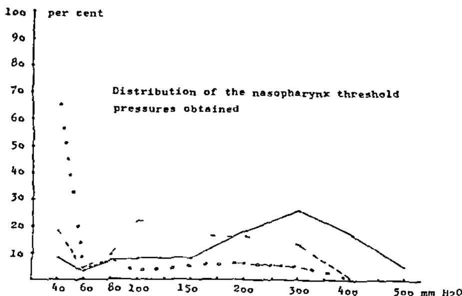


Fig 5 Curves 1 og 2 from a normal middle ear

—— Cleft palates series
Writer s series of normal children
o o Thomsen s series of normal adults

that during the overpressure established in the middle ear the tympanic membrane is pressed outwards, thus giving an alternation in the acoustic impedance

By calibrating the impedance meter it is possible exactly to registrate the size of the overpressure that even in a very short moment occurs in the middle ear Thus the pressure occurring in the middle ear immediately after the admittance of air is measured Furthermore is measured the maximal middle ear pressure which is held without swallowing, and finally the levelling pressure and numbers of deglutitory movements necessary for obtaining the final stationary pressure

Fig 4 shows better than many words, how variations in impedance are registered at an insufflation of air from the nasopharynx Immediately after a myngographic recording the apparatus is calibrated by altering the pressure difference between middle ear and auditory meatus, and thus measuring the corresponding variations of the acustic impedance This is seen in the second curve from above Furthermore is seen the tympanometric curve from a patient with normal hearing and normal middle ear pressure Here the pressure in the external auditory meatus is variated, and an impedance minimum is found at a pressure of zero in the ear canal

Curves c and d are from a patient suffering from adhesive otitis No impedance minima are found by the tympanometric test, whereas a deglutitory movement against a big overpressure in the nasopharynx makes an alteration in the impedance of short duration as indication of tubal passage

Fig 5 gives an impression of the threshold pressures in 1 the series of children with cleft palate, 2 the series of normal children from 7 to 14 years of age and 3 Thomsen's series of adults It appears that the threshold is rather high in the

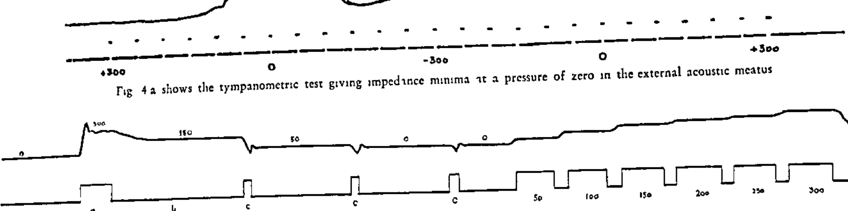
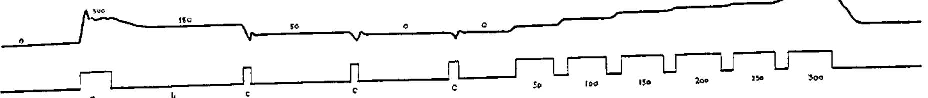
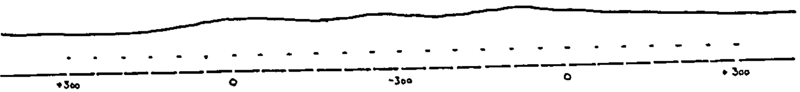


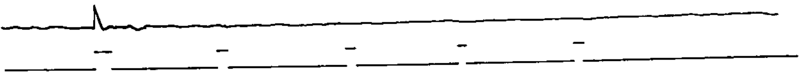
Fig 4 a shows the tympanometric test giving impedance minima at a pressure of zero in the external acoustic meatus



a s p = 30 mm H_2O

Fig 4 b shows impedance variations, when swallowing against a rhinopharynx pressure of 300 mm water (a application of rhinopharynx overpressure, b decreasing pressure in the middle ear to stationary value, c deglutitory movements) Right is seen the calibration of the impedance meter For further details see text





a d p = 500 mm H_2O

Figs 4 c and 4 d obtained from a patient with adhesive otitis showing no impedance minima at the tympanometric test shown in Fig 4 c, whereas a short alteration of impedance is seen, when swallowing against a high overpressure in the rhinopharynx (Fig 4 d)

OTITIS MEDIA CATARRHALIS AND DENTAL CARIES

By
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Abstract

In a group of patients with otitis media catarrhalis a search was made for the ecto-mesodermal syndrome which has primarily been demonstrated in patients with otosclerosis In collaboration with the school dentist, attention was especially focused on the dental system using dental caries as an indicator The study shows that a constitutional factor in the ecto- and mesodermal organ may in some cases be responsible for the development of chronic otitis media catarrhalis.

In the study of the ecto-mesodermal syndrome and its possible relation to defects in the middle and inner ear, we have included the dental organ In the ecto-mesodermal syndrome we include clinical symptoms from the ectoderm (epi dermis, hair, nail, and dental enamel) and mesoderm (corium, vessel, tendon, joint, bone, dentine, and cementum) It has been demonstrated that some patients with otosclerosis have this syndrome with ectodermal symptoms such as thin, silky hair, brittle nails, and mesodermal symptoms, such as a tendency to subcutaneous bleedings, excessive laxity of the joints and brittle teeth with a tendency to dental caries (Bentzen, 1962) Since 1958 biopsy specimens of the skin have been taken from the extensor side of the upper arm in such patients These showed abnormalities in the subcutaneous tissue, viz increase of the acid mucopoly saccharides, rarefaction of the reticular fibrils and fragmentation of the elastic fibres (Bentzen 1961, Stadil 1961) Abnormalities of the skin vessels in otosclerosis (Vyslonzil, 1956), mesenchymal hypoplasia in skin biopsies in otosclerosis (Liverero & Loggia, 1962), and trisomy and tetrasomy for chromosome no 13 have been observed in patients with otoslerosis and their relatives (Tato, de Lozzios & Valencia 1962)

In patients with cleft palate, an increased frequency of suppurative and non-suppurative otitis media has been revealed (Paulsen, 1963) and the pneumatiza tion of the temporal bone has been demonstrated to be strikingly abnormal in most cases (Harvold, 1954) In the same series a defect in the second molar of the lower jaw was frequently demonstrated and recently an analysis of the dental organ in patients with cleft palate showed a strong tendency to affection in all teeth (Bohn 1963)

The ecto-mesodermal syndrome was demonstrated very clearly in a girl with cleft palate, suppurative otitis media of the left ear and abnormalities of the dental organ At the age of four, there was extensive destruction of the teeth as

childhood, and that children with cleft palates show a higher threshold pressure than normal children of the same age No correspondance between threshold pressure and hearing level is found in the series investigated Nor did the investigation prove a relationship between the tubal valve function from middle ear to nasopharynx and vice versa In a few cases with high threshold pressures for tubal passage a high stationary middle ear pressure is found together with poor levelling of the pressure between the middle ear and nasopharynx at several deglutitory movements and high final middle ear pressures

Finally Toynbee's test is carried out on 27 patients, and the test was positive in 60 % of the cases This is congruent to the frequency in the normal series of children, but it seems a little lower than in Thomsen's series, where the Toynbee test appeared positive in 72 %

From this investigation it can be concluded that the stenosis of the Eustachian tube is rare, and that the most common factor found is an occlusion of the tube, probably because of muscular malfunction giving a poor equalisation of pressure from rhinopharynx to middle ear

In one case, the patient being a boy of 13 years, with normal hearing, a patent Eustachian tube was present on the right ear

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Table I *Frequency of dental caries in 14 children with bilateral malignant otitis media catarrh and in 487 children without that disease*

Defective teeth	Otitis media catarrh (14 children)	No otitis media catarrh (487 children)	
No	No	No	%
16	1	38	8
15	2	29	6
14	3	46	9
13	2	47	9
12	2	89	18
11	2	60	12
6	1	15	3
3	1	7	1

The series with recurrent or chronic otitis media catarrhalis seems to show a tendency to a higher frequency of dental caries than the children without that disease

Table II *The severity of caries in the series with otitis media catarrh and in the 487 children without that disease*

Defective teeth	Severity of caries	Otitis media catarrh. (14 children)	No otitis media catarrh. (487 children)
No			
16	Total	1/14	38/487 8 %
12	3/4	10/14	249/487 = 50 %
11	2/3	12/14	309/487 62 %

The severity of the ear disease and the results of dental examination are illustrated in the following case histories

Case 1 H B E, girl, 9 years father post-office clerk At school, she was unable to keep up with the rest of the class During the last three years she had for several periods been treated by an otologist at the request of the school doctor At the age of 9, examination in the Department of Otology revealed chronic maxillary sinusitis and chronic otitis media catarrhalis on both sides

Dental status (9 years) Very severe caries involving 14 teeth

Case 2 K.D E, boy, 14 ears father dock worker From the age of 9 to 13 the boy had, for two periods every year, been treated for recurrent hearing impairment by an otologist at the request of the school doctor

Dental status (8 years) Extremely severe caries of all 16 teeth

Case 3 S A , girl, 12 years, father mechanic From the age of 7 to 9 years, she had, for several periods, been treated by an otologist for impaired hearing and retracted tympanic membranes on both sides

Dental status (7 years) Severe caries of 12 teeth

The next two cases of severe otitis media associated with dental caries were observed in the same family The fathers of the patients were brothers

Case 4 K E J , boy, 11 years, father mechanic At 8 and 10 years, he was treated by an otologist for retraction of the tympanic membrane at the request of the school doctor, who had disclosed defective hearing

Dental status (8 years) Caries of 13 teeth

Case 5 N A J , boy, 11 years, father lorry driver At 8, 10 and 11 years, the patient was, for several periods, treated by an otologist for retraction of the tympanic membranes The school doctor had revealed impaired hearing on several occasions

Dental status (8 years) Very severe caries involving 15 teeth

Dental examination revealed that, with the exception of four, each of the children with severe otitis media catarrhalis had at least 12 affected teeth In the control series, only 50 % of the children showed equally severe caries

The next two patients with severe otitis media had very fine teeth

Case 6 O H L , boy, 10 years, mother nurse At the age of 7 and 8 years, he had for three periods been treated by an otologist at the request of the school doctor

Dental status (8 years) Only six out of the 16 teeth were affected with caries his dental status was the fourth best in his class of 22 pupils

Case 7 B H , girl, 12 years, father oil worker On several occasions, audiometry at school had revealed hearing loss, for which she had been treated by an otologist At the age of 11 years examination in the Department of Otology revealed retracted tympanic membranes, and a diagnosis of recurrent bilateral otitis media catarrhalis was made

Dental status (8 years) Excellent teeth, caries of only three of the 16 teeth, i e her dental status was the second best in her class of 11 pupils

The examination for dental caries in 14 children with severe bilateral otitis media catarrhalis showed that 12 children had more and two children less caries than the control group of 487 children without this middle ear disease

A possible explanation of these findings may be the presence of a host factor responding with chronic abnormalities to acute infections in the middle ear and in the dental organ with severe caries to ordinary factors causing dental caries In the aforementioned case of cleft palate with a combination of chronic otitis media and caries abnormalities in the skin hair and congenital defects of hands and feet in the family this host factor is constitutional Cases associated with abnormalities in the dental organ and a tendency to chronic otitis media catarrhalis in families with other symptoms from the ecto-mesodermal syndrome would support the presence of such a factor

Two cases of otitis media catarrhalis chronica in families, with symptoms from the ecto and mesoderm

Family 1

A boy, 14 years old, having two normal sisters, a normal brother and a half-brother with bilateral suppurative otitis media, had since the age of 11 years suffered from bilateral otitis media catarrhalis The ear disease had very often been treated by the otologist at the request of the school doctor, who found recurrent hearing impairment The mother of all the children has bilateral suppurative otitis media The status of the middle ear and dental system in the family is seen from Table III

T a b l e III *Dental system (no /16) indicate number of defective teeth in the age of 7—8 years *) Not examined*

Person	Otitis media	Dental system	Remarks
Patient	Bilat catarrh. chr	fine (3/16)	hyperflex of thumbs
Half brother	Bilat suppurat chr	fine (8/16)	
Sister *)	No	fine	
Sister *)	No	fine (2/16)	
Brother *)	No	fine (1/16)	
Mother	Bilat suppurat chr	?	blue sclerae triangular face

The dental examination of the patient and his half brother at the age of 7—8 years showed mild caries, especially in the patient, in whom only three teeth of the 16 were affected He has abnormal mobility of both thumbs The mother has triangular face and blue sclerae as seen in some syndrome of connective tissue, especially in osteogenesis imperfecta

Family 2

A boy, 8 years old having two siblings with normal ears and three with suppurative otitis media, had since the age of 7 years otitis media catarrhalis Like the mother the patient has a marked tendency to subcutaneous bleedings, and silky hair Like some of the siblings he has slight abnormalities of the hands and feet The mother of all the children suffers from suppurative otitis media of the right ear The status of the middle-ear, dental system and symptoms from the ecto and mesoderm in the family is shown in Table IV

The dental examination of all the children, based on the records from the school dental clinic and the present status based on personal examination, showed very severe caries in patient, and in his siblings Nothing is known about the mother, but she has worn a complete prosthesis of the upper jaw since the age of 17 and of the lower jaw since the age of 19 years The mother has blue sclerae

The two patients with severe bilateral otitis media catarrhalis and bilateral

Table IV *Defective teeth (no /16) indicate number of defective teeth in the age of 7—8 years Servity of caries +++ indicate the present status of the dental system Other defects H = hands, F = feet S = skin Ha = hair *) Not examined*

Person	Otitis media	Defective teeth	Severity of caries	Other defects			
				H	F	S	Ha
Patient	Bilat catarrh. chr	13 16	+++	+	+	+	+3
Brother	Left suppurat chr	12/16	++	+	+		
Half sister	Bilat suppurat chr	10/16	++				
Half sister	No	9 16	— +		+		
Half sister *)	Bilat suppurat chr	9/16		?	?	?	?
Half brother *)	No	9/16		?	?	?	?
Mother	Right suppurat chr		?	+		+	+

hearing defect in the two families have the combination of otitis media and an "extremely good" (family 1) and extremely bad (family 2) dental system In both cases there is a family tendency to middle ear affection and symptoms from the ecto and mesoderm especially in family 2 The patient in this family has the symptoms of the ecto mesodermal syndrome as we have seen them in many patients with otosclerosis These symptoms associated with histological abnormalities in the skin is in support of the assumption that otosclerosis should be included among the mesenchymopathies with a generalised anomaly of the con nective tissue This hypothesis had been suggested by many authors (Arsland & Ricci, Simson Hall)

CONCLUSIONS

From the school health service it is known that some children show a tendency to chronic recurrent otitis media catarrhalis The same tendency is seen in children with cleft palate, i e children who often have a strikingly abnormal pneumati zation of the temporal bone and a great tendency to abnormalities in the dental system These symptoms may suggest the existence of a constitutional factor

In order to investigate if such a constitutional factor could be responsible for the development of the chronic otitis media catarrhalis, the dental system in 14 children with this disease was examined

They seem to have a relatively higher frequency of dental caries than found among their schoolfellows Two children with chronic otitis media catarrhalis, in families with a tendency to chronic otitis media — one has an abnormal high the other 'abnormal" slight degree of caries In the families there are symptoms from the ecto and mesodermal organ, such as thin silky hair, tendency to subcutaneous bleedings and defects in the feet and hands

The study shows that a constitutional factor in the ecto and mesodermal organ may in some cases be responsible for the development of chronic otitis media catarrhalis

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ADHESIVE OTITIS MEDIA IN AUDIOI OGY

By

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Abstract

The treatment of and the difficulties in the diagnosis of adhes ve otitis med a are elucidated from an audiological point of view 10 % of the 39 000 patients in the State Hearing Center of Copenhagen are labeled adhesive otitis but many can be divided in sub groups through further examination

In the Danish State Hearing Centres we have from the beginning in 1951 kept a list of common diagnoses in order to obtain a statistic covering the whole country with regard to the incidence and the kind of hearing disorders

60 % of the adult patients in Copenhagen are pure perceptive cases, and among the conductive cases we distinguish among the following groups

Otitis media chronica adhesiva	=	10 %
Otitis media chronica perforative	=	12 %
Otitis media chronica suppurativa	=	4 %
Otosclerosis	=	13 %
Seq resect auris mediae tot	= ca	1 %

Adhesive otitis might for a great deal be substituted by the diagnosis seqvelae otitidis, but from an audiological point of view we just want to exclude patients with dry perforations of the drum, because the sound waves in these cases directly hit the fenestra rotunda et ovalis

The definition of the diagnosis adhesive otitis is not clear, but in our clinic we make use of it, when none of the other conductive diagnoses can be applied, and our diagnosis is based upon case history — otoscopy — hearing examinations

Case history The patient may have had one or more attacks of otitis of either bacterial origin or just non baterial catarrhal otitis, eventually on an allergic basis

Otoscopy The drum may be scarred, have stains of chalck, be uniformed fibrous or have a nearly normal appearance as we quite well may have adhesions among the ossicles alone or among these and other parts of the tympanic walls of which the membrane only is about 1/7 Siegl s otoscope is of great value, and as a rule it shows reduced mobility either of the membrane or of the manubrium, possibly of both

The effect of tubar insufflation and the quality of the whistling sound give information whether the passage through the Eustachian tube is impaired or totally occluded If the function of the tube is normal but no hearing improve-

ment takes place in connection with the insufflation, this indicates fixative processess in the middle ear

Hearing examinations Pure tone audiometry may show a clear conductive disorder with bone conduction values about normal threshold or the bone conduction values may be lowered, f i in connection with adhesive processes around the oval or the round window, which alters the mechanical conditions in the inner ear so that the bone conduction values do not properly express the functioning of the organ of corti Speech audiometry is important and a 100 % discrimination indicates a normal inner-ear

The diagnosis adhesive otitis is not well defined, but depends on the above mentioned clinical observations It is possible to obtain a further differentiation through the following additional examinations

Impedance measurement
X ray examinations, possibly polytomy
Explorative tympanotomy

The following diseases should be considered in the differential diagnosis
Developmental anomalies
Traumatic luxation (possibly in connection with unsuccessful paracentesis or resection of the mastoid process)
Old secretion in the tympanic cavity
Tympanosclerosis
Ectopic (or primary) cholesteatoma
Otosclerosis

In the daily work of the hearing centre the impedance measurement is our method of choice We get information about the patency of the Eustachian tube, about the middle ear pressure, and we get a certain estimate of the aeration in the middle ear with its connected cellulae Our experience shows that otosclerosis is most likely to exist, when there is a normal function of the tuba and a normal aeration, but no reflexes

Treatment is to begin with otological, and if this does not restore hearing, the audiological treatment follows These patients belong to our most grateful group, because their only need is one or two head worn hearing aids which give a certain amplification of sounds and language discriminated faithfully by the normal inner ear

In the State Hearing Rehabilitation Centre in Copenhagen we have now treated 35 000 patients with hearing disorders (32,800 adults — 2,200 children) About 10 % — 3,500 patients are hard of hearing due to adhesive otitis No doubt this number can be reduced and must be reduced considerably through a more active otological treatment and a more effective control till full recovery

THE USE OF POLYETHYLENE TUBES IN SEROUS OTITIS MEDIA

By

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Serous otitis media (SOM) is a condition which presents considerable problems to the otologist The majority of cases occur in children, when the commonest cause is occlusion of the eustachian tube from enlarged adenoids Adenoidectomy also cures the SOM in most cases, especially if the operation is accompanied at the same time with myringotomy and aspiration of the effusion from the middle ear Other cases of SOM are cured by the treatment of other causes of tubal occlusion, such as sinusitis, chronic tonsillitis, chronic rhinitis, deformities of the septum, nasopharyngeal neoplasms metabolic disorders, heart and kidney diseases, etc

After all conventional methods and measures have been employed to remove the causes of SOM, there nevertheless often remain some patients whose condition has not been cured These patients have the disease in what is known as chronic form The really difficult problems are connected with the treatment of these cases, and it is precisely with the treatment of these chronic cases of SOM that the present paper is concerned

In 1954, Armstrong described one method of treating cases of SOM which fail to respond to conventional treatment The method involves the insertion of a small vinyl tube into the middle ear through a conventional myringotomy incision The tube is left in place until the symptoms of SOM have subsided The use of plastic indwelling tube has subsequently been briefly mentioned by Goodhill (1957, 1958), Burton & Wright (1916) Bell (1961) Boor (1962) and Lemon (1962)

THE METHOD

The present writer has used a polyethylene tube, inserted into the tympanic cavity, in the treatment of 25 patients with chronic SOM The tube was made for the purpose by Richards Manufacturing Company (Memphis) to specifications by Shea It is 7 mm long 1 mm in diameter, and is fitted with a flange to keep it effectively in position in the tympanic cavity

The ear canal was first cleaned mechanically and then sterilized with 70 per cent alcohol The drum was anaesthetized with Xylocain spray, and anaesthesia was allowed to take for 15 minutes Myringotomy in the inferior part of the drum was performed under a Zeiss operating microscope with 10x magnification Another point like myringotomy was made in the anterior inferior quadrant of the drum to allow the passage of air when effusion was aspirated by spot suction, through the first aperture Subsequently the polyethylene tube

was inserted through the myringotomy aperture, which had been made the exact size to allow the flange to be pressed into the tympanic cavity. The other end of the tube was bent forward so as to support itself against the anterior wall of

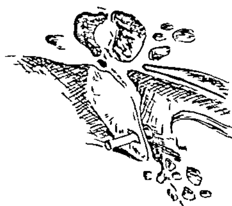


Fig 1 The flanged indwelling tube in position

the ear canal, thus remaining safely in position After the insertion of the tube patient was allowed to go home and requested to return for a check up after one month, or sooner if symptoms of SOM recurred Patients were not recommended to practise the Valsalva inflation at home

THE SERIES

The number of patients treated was 25, of whom 9 were women and 16 men Distribution by age is shown in Table I

Table I *Distribution of the patients by age*

Age Years	Number
5	2
6 10	12
11–15	2
16–20	2
21 25	0
26–30	3
31–	4

The youngest patient was 3 years old, the oldest 52 Eighteen patients had bilateral and 7 unilateral SOM, and the total number of ears treated was thus 43 *Three of the patients treated for unilateral SOM showed pathological changes* in the contralateral ear One of them had adhesive otitis in terminal stage while 2 had undergone radical ear surgery Roentgenological examination showed a sclerotic, non pneumatized mastoid process in 31 of the 43 ears treated, and a

simple mastoidectomy was performed on these 31 ears before the tube treatment was started Twelve of the 31 ears operated on were found to be affected by chronic latent mastoiditis The remaining ears showed effusion and a thick, in some cases granulating, mucosa in the antrum, aditus and the few air cells Mastoidectomy was performed by postauricular approach The operation cavity was connected with the tympanum via aditus A polyethylene drain was placed through the skin incision into the antrum, after which the skin and periosteum were sutured over the operation cavity, with the drain protruding from the lower end of the incision The drain was removed 8 days after the operation on the day the patient was discharged from hospital

Eleven patients in the series had had symptoms of SOM from 1 to 3 years and 9 patients for more than 3 but less than 6 years In 2 cases the symptoms had lasted from 7 to 9 years, while 1 patient had had symptoms for 12 years, 1 for 15 and 1 for 20 years

RESULTS

For 14 patients the tube treatment was discontinued because the symptoms of SOM disappeared Since the completion of treatment these patient have been free from symptoms for a minimum of 8 months Eleven patients are still being treated For the patients whose treatment has been completed the treatment lasted, on an average, 8 2 months The shortest period was 1 month and the longest 20 months Four tubes were removed from the ear 2 because the treatment was completed and 2 because the lumen of the tube blocked The removal was easy and caused no pain All the remaining tubes were spontaneously ejected An average of 1 8 insertion were required before the treatment of the ear was completed, the maximum required was 5 insertions The tube was replaced immediately if effusion recurred after its ejection or removal

For all the 11 patients still under treatment or whose treatment has recently been completed treatment started within the last 8 months These patients, however, have good hearing and no effusion, thanks to the polyethylene tube

The 3 patients who had had their symptoms for 12, 15 and 20 years, respectively, are in the group whose treatment has been completed The patient with the 12 year history had in his contralateral ear an adhesive process in terminal stage which could not be treated with a polyethylene tube In the treated ear the effusion has disappeared and the tubal function is good though the audiogram shows a small air bone gap, evidently the result of adhesions in the tympanic cavity or rigidity in the ossicular chain His hearing has improved greatly The patient with the 15 year history also has no more effusion Both eustachian tubes open on physiological pressure differences while the audiogram shows a small air bone gap His hearing has definitely improved The patient with the 20 year history is symptom free and the audiogram shows no air bone gap All three patients underwent mastoidectomy before the tube treatment started the actual number of ears treated in this group of "long history" patients was 5 Mastoidectomy revealed chronic latent mastoiditis in 2 cases of this group

Audiograms prior to treatment mostly showed a conductive loss of 20—30 db In 1 case the conductive loss was 40 db, this had been completely offset by the end of treatment Audiological examination may in some cases indicate a false nerve-deafness with a lowered bone conduction curve, apparently because effusion affects the fenestral function (Goodhill, 1957) The bone conduction curves in such cases are restored to normal once the effusion has disappeared

DISCUSSION

The present writer particularly wishes to emphasize the importance of performing mastoidectomy in SOM if x ray examination shows a sclerotic, non pneumatized mastoid process Chronic latent mastoiditis is frequently present in these cases — in the present series it was found in 12 out of 31 ears The remaining 19 ears operated on showed a thickened mucosa and effusion The result of operation is hard to predict in cases such as the latter, but mastoidectomy in these cases of SOM (and in cases of chronic latent mastoiditis) has proved to be useful from another point of view During the operation the thick mucosa (or granulations in chronic mastoiditis) is removed from the antrum, aditus septa and cells, and an operation cavity with smooth walls achieved The cavity will later be lined with a thin mucosa containing fewer blood vessels than the removed mucosa Furthermore, the mucosa in the tympanum and the operation cavity will now have a considerably smaller surface compared with the quantity of air than preoperatively, and resorption of this air will therefore take place more slowly If effusion recurs after mastoidectomy a polyethylene tube should immediately be inserted through the drum into the tympanic cavity The tube will keep the pressure in the middle ear normal The smaller the underpressure in the middle ear the more easily is the eustachian tube opened by the slight overpressure in the nasopharynx on swallowing This overpressure cannot increase physiologically When the treatment with an indwelling polyethylene tube has been completed conditions in the operated middle ear are then the most favourable possible for the resumption of normal functioning by the eustachian tube The necessity of mastoidectomy in certain cases of SOM has been mentioned by several authors (Jervey 1922, Cody 1941, Robison 1942, Hitschler 1955, Singleton 1956, Goodhill 1958)

In all the present cases of SOM the eustachian tube was patent as tested by Politzer's method In many cases the tube was opened also by Valsalva's manoeuvre Both methods, however, make use of an overpressure in the nasopharynx considerably in excess of the slight physiological overpressure caused in swallowing It is therefore of little significance to ensure that the eustachian tube in many cases of SOM is easily patent tested by Politzer's or Valsalva's manoeuvre or by catheter In no case was the eustachian tube opened preoperatively by Toynbee's manoeuvre in which very small pressure differences are employed

Many authors have stressed the importance of a middle ear ventilation of longer duration than that obtained by myringotomy and aspiration of effusion in order that the conditions in the middle ear be normalized Making a permanent

perforation in the tympanic membrane has been recommended by Milligan (1921), Claus (1930), Hotchkiss (1948) Robison & Nicholas (1951) and Singleton (1952) Such "permanent perforation however usually heals before the eustachian tube is opened, as was pointed out by Milligan as early as 1921

Nothing definite is known of the etiology of the disease but any condition that contributes to swelling and closure of the eustachian tube may be a factor in the production of SOM It is recognized, however, that not all cases of occluded eustachian tube develop into SOM (Zollner 1936, van Dieshoeck 1941, Carpenter 1949 Hoople 1950) Other factors must apparently coincide, and two of the most important are allergy and infection The part played by allergy however, is disputed In the present series no appreciable degree of allergy was demonstrable This accords with opinions advanced by Carpenter (1949), Robison & Nicholas (1951), Fishman Lennette & Dannerberg (1960), and Lemon (1962) but other authors have been able to demonstrate the influence of allergy in SOM (Hoople & Blaisdell 1943, Dohlman 1943, Jordan 1949, Solow 1958, and Jones 1959) An allergic mucosa is naturally highly susceptible to infection and harder to rid of infection The few cases of allergy in the present series also showed infection Chronic latent mastoiditis existed in 12 ears In many cases the symptoms of SOM started in conjunction with an acute infection of the upper respiratory tract In 3 of the unilateral cases there was or had been chronic inflammation in the contralateral ear No systematic bacterial studies were carried out during the treatment of this series It is worth reporting, however, that in 3 cases of latent mastoiditis bacteria (Staphylococcus aureus, Pneumococcus) could be cultured from the granulations but not from the effusion This concurs with Forschner's (1925) observations and must be attributable to the fact that effusion in SOM contains substances that inhibit bacterial growth The bacteriostatic effect of the exudate in acute otitis media has been demonstrated by Siirala & Lahikainen (1952) and Siirala & Vuori (1954) A number of authors have found bacteria in the effusion in SOM (Forschner 1952, Blegvad 1931, King 1953, Senturia, Gessert, Carr & Baumann 1958) Most observers have considered the effusion to be sterile (Scheibe 1889, Dohlman 1943, Hoople & Blaisdell 1943, Shaninian 1943, Ivstam 1954, Theobald 1958, Lemon 1962)

On the length of time for which the tube was left in position, Armstrong reports in his earlier paper (1954) that 2—3 weeks had been long enough in most cases while in a later paper (1957) he says that the tubing may be left in place from 1 week to 3 months or longer depending upon the duration of the disease and the clinical response Armstrong used tubes of vinyl which like the polyethylene tubes employed by the present writer, belong to plastics Armstrong assumed in 1954 that a permanent perforation in the tympanic membrane may be obtained if the tube is left in place over a long period of time, but in 1957 he found that no permanent perforation had resulted Nor has permanent perforation resulted in any case of the present series despite the fact that a tube has been left in place for up to 20 months

Although the tube is inert to tissue it is still a foreign body which the tissues generally tend to expel If the tube has been expelled and the disease has not been

cured the patient will immediately notice that effusion has recurred and he can return to have the tube replaced In the present series, the tube once expelled was re-inserted exactly where it had previously been in the tympanic cavity No damage to the mucosa of the tympanic cavity was evident In 1 case the particularly thick glue like effusion could not be aspirated in the ordinary way, and a bilateral tympanotomy was considered necessary, on which the glue like matter in the eustachian portion of the tympanic cavity could be removed A 15 mm long polyethylene tube, 1 mm in diameter, was inserted in the tympanic cavity through the incision in the ear canal The tubes are still in position, and the patient is symptom free, with normal hearing Both eustachian tubes can now be opened by Toynbee's manoeuvre Tympanotomy in SOM with glue-like effusion has previously been described by Colman (1958) and Bauer & Wodak (1961)

In general, no antibiotic therapy was given while the tube was in position Three patients contracted acute otitis during the treatment, 1 patient in connection with chickenpox and 2 in connection with an acute infection of the respiratory tract These 3 patients had also had otitis, in connection with respiratory tract infections, before the tube treatment

Treatment of SOM with indwelling tubes is effective as long as there are no irreversible changes in the tympanum It is of course, important to treat a latent mastoiditis prior to inserting the tube As has been pointed out by Politzer in 1867 and by other authors more recently (Lumio 1951, Ojala 1953, and Siirala 1960), SOM if not treated or refractory to treatment is transformed into chronic adhesive otitis This involves reduced hearing the improvement of which sets the otologist extremely difficult problems It seems, however, that in many cases of SOM irreversible changes begin in the middle ear only after effusion has persisted for several years For the prophylaxis of SOM it is important that myringotomy be performed in acute otitis and that the hearing is checked after the otitis has healed It seems as if the widespread, inadequate use of antibiotics in simple upper respiratory tract infections might be one of the reasons for the increased incidence of SOM

SUMMARY

With all the available surgical technique and other conventional methods for combatting the cause or causes of serous otitis media, there always remain some patients who have not been cured The present author has treated 25 such chronic cases by inserting a flanged polyethylene tube in the tympanic cavity through an incision in the tympanic membrane according to an idea suggested by Armstrong The importance of mastoidectomy to overcome a latent mastoiditis is emphasized The treatment of 14 patients has been completed and the patients' progress has been followed for a minimum of 8 months In these patients the symptoms of serous otitis media have disappeared The treatment of 11 patients still continues or has only recently been completed These patients too, have been symptom free during the period of treatment

ZUSAMMENFASSUNG

Wenn alle die herkommlichen Methoden zur Behebung der Ursache oder Ursachen der Otitis media serosa angewandt worden sind, bleiben immer noch manche Patienten ubrig, deren Krankheit nicht geheilt werden konnte Der Verfasser hat 25 derartige chronische Falle behandelt, indem eine kleine, mit einer Manschette versehene Polyethylentube so durch eine Inzision im Trommelfell geschoben wurde dass das eine Ende in die Paukenhohle und das andere in den Gehorgang ragte Die Idee ist von Armstrong beschrieben worden Die Bedeutung einer Mastoidektomie zur Behebung einer gleichzeitig bestehenden latenten Mastoiditis wird hervorgehoben Bei 14 Patienten ist die Behandlung nunmehr abgeschlossen die Observationszeit war mindestens 8 Monate Die Symptome der Otitis media serosa sind bei diesen Patienten abgeklungen Bei 11 weiteren Patienten ist die Behandlung noch im Gang oder wurde erst kurzlich abgeschlossen Auch diese Patienten sind im Lauf der Tubenbehandlung vollig symptomfrei gewesen

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TRANSMYRINGEAL PERMANENT DRAINAGE IN CHRONIC SECRETORY MIDDLE EAR DISEASE

By

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Abstract

A transmyringeal polyethylene tube was used in different problematic cases of chronic serous middle ear diseases such as idiopathic haemotympanum and chronic secretory otitis media With this arrangement for permanent drainage lasting normalization of the middle ear function was obtained

INTRODUCTION

The management of difficult cases of chronic serous middle ear diseases by inserting a permanent drainage is not a new idea, nor is the use of a transmyringeal polyethylene tube for this purpose There is evidence suggesting that the technique has been applied previously but the published work amounts to little more than a few isolated casereports (Armstrong 1954, Sheehy & McKibben, 1956) Armstrong (1957) is the only author to have dealt in any length with the possibilities of the method, and the results achieved with it are described as very good On the other hand, the few cases reported in detail suggest that other therapeutic measures such as adenoidectomy may have been used at the same time, so that it is difficult to judge the effect of the permanent drainage itself The general impression is, however, a good one, and the familiar problems presented by the treatment of such cases seemed to warrant a critical and consistent testing of the method

A study was accordingly designed to examine the extent to which long term treatment with a transmyringeal polyethylene tube may be of value in cases of chronic otitis media that had proved resistent to all the more common forms of therapy such as adenoidectomy, paracentesis, air insufflation, various medical treatments and to some extent even radiotherapy Special attention was devoted to the possible disadvantages and complications such as discomfort, obstruction of drainage, detachment of the tube, inflammatory exacerbations and persistent perforation of the tympanic membrane

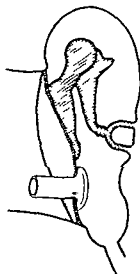
Of the ear diseases for which this form of treatment may be suitable ordinary chronic otosalpingitis is the most important, not least because it most commonly afflicts children and then it presents especially great problems The hearing loss is often sufficiently pronounced and persistent to create various difficulties especially at school There is often a troublesome pressure sensation and sometimes painful inflammatory episodes The numerous time consuming visits to the

doctor often constitute a disturbing factor and may lead to a fear of the doctor and a mental fixation with regard to the ear disease with a tendency to psychogenic complications Finally, there is a risk that the chronic otosalpingitis will develop into chronic adhesive otitis and hence practically irreversible hearing loss

Even in the extremely difficult case of chronic otosalpingitis, however, there is, particularly among children, a capricious spontaneous course, an improvement with age is not uncommon and may appear unpredictably It is therefore particularly instructive to explore the effect of tubing drainage on the adult with chronic otosalpingitis due to a more specific and irreversible dysfunction of the Eustachian tube and cases of idiopathic haemotympanum — the rare but well defined variant of chronic middle ear catarrh, which is especially known for its tenacious resistance to therapy Burton & Wright (1961) reports one case of idiopathic haemotympanum in which the tube technique resulted in normalization for a period of some weeks On the other hand no mention is made of the long term development

MATERIAL

The series consists of 13 specially stubborn cases of chronic middle ear catarrh, *10 of them children aged 3—13 years and 3 adults Two of the children had* unilateral idiopathic haemotympanum and one of the adults had unilatera



chronic otosalpingitis owing to dysfunction of the Eustachian tube following irradiation of a tumour of the epipharynx The others were less specific cases of chronic otosalpingitis All had a hearing loss of the conductive type of such severity as to cause long term problems and in all there had been persistent attempts at treatment with all the usual forms of therapy, usually over several years without success

TECHNIQUE

The permanent drainage consisted of a polyethylene tube PE 90, length 4 mm, width 0 86 by 1 27 mm At first the tube was used in its original form but on the basis of experience the inner orifice was widened concentrically to a diameter of about 3 mm, this was done by warming near a flame The tube was placed normally in a paracentesis in the posterior inferior quadrant of the tympanic membrane but in cases in which the membrane was severely atrophied, it was placed in the least involved part of the membrane (see Fig) The operation may be performed without anaesthesia but as a rule local anaesthesia was used for adults and general anaesthesia for children An operation microscope was used throughout

RESULTS

In all cases intubation resulted almost immediately in complete normalization of the middle ear function and absence of any discomfort The favourable effect remained so long as the drainage was maintained The period of observation up to the time of this report is 2—17 months At first there was often an increase in the secretion, with was not, however, accompanied by any discomfort and in all cases ceased In some cases symptoms of acute otitis appeared during treatment but recovery was rapid with the usual conservative therapy, and without it being necessary to remove the tube Obstruction of the tube was observed in only one case, and the passage was easily restored by gentle suction after instilling hydrogen peroxide in the meatus The straight tube that was used at first usually fell out after 1—3 months The tympanic membrane healed in a short time and there was a chronic relapse, which, however, was successfully treated by inserting a new tube with a widened internal aperture In most cases a tube preformed in this way is still in place and functioning properly, in some cases more than 6 months since insertion In two cases, however, this type of tube also came away, but not for at least 3—4 months A new tube was then immediately inserted owing to relapse when the ear-drum healed

Since the treatment was succesful in all cases it will suffice to report two representative ones

Case 1 — A.N a boy aged 13 years who for the previous 5 years had been receiving treatment for chronic otosalpingitis with severe conductive hearing loss in the right ear Radiographs of the sinus and ear and an allergy examination revealed nothing remarkable Radiotherapy was performed with no positive results Som 50 paracenteses had been performed by various doctors and there was often a normalization of the hearing but it lasted only a couple of days After 4 years of treatment the boy had gradually become afraid and neurotic Tympanotomy was performed but apart from an accumulation of secretion the findings were unremarkable During the last 12 months the treatment had been discountinued so as to avoid further mental disturbance

The insertion of a pre formed tube resulted in lasting normalization of the hearing and freedom from discomfort This situation has now remained for the past 8 months Short periods of mild secretion with no discomfort were experienced during the treatment For the last 4 months the boy has been allowed to bathe and even d p his head without complications developing Thus,

in spite of the presence of the tube the ear feels and functions as normal and the problem would seem to have been eliminated, maybe until such time as there is a spontaneous improvement of the basic condition

Case 2 — I.R., a boy of 12 years, who since the age of 7, had been recognized as a typical case of right sided idiopathic haemotympanum The usual forms of treatment had been tried over long periods but without results Finally, mastoidectomy was performed, a measure that has been reported in some cases to lead to recovery from these conditions (Menck Thygesen, 1952, Hall, 1957, Sheehy & McKibben, 1961) The cell system was extremely small and the findings were typical of such cases, namely granulation tissue with bleeding points and a chocolate coloured abacterial secretion The microscopic findings were also typical — cholesterol crystals with giant cells and other signs of foreign body reaction Nor, however, did the surgical treatment result in recovery

On inserting a straight polyethylene tube the hearing was immediately normalized in spite of the fact that for the first two months there was a copious thin secretion, there was, however, no discomfort During the next two months there was no secretion and the ear felt and functioned normally in all respects At the end of the fourth month the tube came free, the tympanic membrane healed and there was a complete relapse After a delay of 2 months a preformed tube was inserted and there was again complete normalization The tube has now been in place for 6 months and there have been no symptoms except for an episode of acute otitis, which ran a brief and mild course

COMMENTS

From the results it is evident that insertion of a polyethylene tube for long permanent drainage is a method that is well worth trying in problematic cases of chronic serous otitis media The treatment, which is purely symptomatic cannot, of course, be considered as a definitive solution of the difficult problem of treatment, but from the practical standpoint it is a real advantage to be able to arrest for long periods the retraction of the tympanic membrane and the accumulation of secretion that causes the symptoms In this way one can avoid futile treatment, while hoping for spontaneous normalization of the basic pathologic mechanism with the course of time

ZUSAMMENFASSUNG

Eine transmyringeale Polyethylentube wurde in 13 besonders problematischen Fallen chronischen Mittelohrkatarrhs wie idiopathischem Hamotympanon und chronischer Otosalpingitis appliciert Die innere Öffnung der Tube war konzentrisch erweitert, um eine Loslosung zu verhindern Die Behandlung resultierte ausnahmslos in einer fortdauernden Normalisierung der Mittelohrfunktion und subjektiver Beschwerdenfreiheit unter Einwirkung der permanenten Dranage, die bis jetzt aufrechterhalten werden konnte, d h in gewissen Fällen langer als ein halbes Jahr

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TECHNIQUE

The permanent drainage consisted of a polyethylene tube PE 90 length 4 mm, width 0.86 by 1.27 mm. At first the tube was used in its original form but on the basis of experience the inner orifice was widened concentrically to a diameter of about 3 mm; this was done by warming near a flame. The tube was placed normally in a paracentesis in the posterior inferior quadrant of the tympanic membrane but in cases in which the membrane was severely atrophied, it was placed in the least involved part of the membrane (see Fig.). The operation may be performed without anaesthesia but as a rule local anaesthesia was used for adults and general anaesthesia for children. An operation microscope was used throughout.

RESULTS

In all cases intubation resulted almost immediately in complete normalization of the middle ear function and absence of any discomfort. The favourable effect remained so long as the drainage was maintained. The period of observation up to the time of this report is 2—17 months. At first there was often an increase in the secretion, which was never, however, accompanied by any discomfort and in all cases ceased. In some cases symptoms of acute otitis appeared during treatment but recovery was rapid with the usual conservative therapy, and without it being necessary to remove the tube. Obstruction of the tube was observed in only one case and the passage was easily restored by gentle suction after instilling hydrogen peroxide in the meatus. The straight tube that was used at first usually fell out after 1—3 months. The tympanic membrane healed in a short time and there was a chronic relapse which, however, was successfully treated by inserting a new tube with a widened internal aperture. In most cases a tube preformed in this way is still in place and functioning properly, in some cases more than 6 months since insertion. In two cases, however, this type of tube also came away, but not for at least 3—4 months. A new tube was then immediately inserted owing to relapse when the ear drum healed.

Since the treatment was succesful in all cases it will suffice to report two representative ones.

Case 1. — A.N., a boy aged 13 years, who for the previous 5 years had been receiving treatment for chronic otosalpingitis with severe conductive hearing loss in the right ear. Radiographs of the sinus and ear and an allergy examination revealed nothing remarkable. Radiotherapy was performed with no positive results. Some 50 paracenteses had been performed by various doctors, and there was often a normalization of the hearing but it lasted only a couple of days. After 4 years of treatment the boy had gradually become afraid and neurotic. Tympanotomy was performed but apart from an accumulation of secretion the findings were unremarkable. During the last 12 months the treatment had been discontinued so as to avoid further mental disturbance.

The insertion of a preformed tube resulted in lasting normalization of the hearing and freedom from discomfort. This situation has now remained for the past 8 months. Short periods of mild secretion with no discomfort were experienced during the treatment. For the last 4 months the boy has been allowed to bathe and even dip his head without complications developing. Thus,

tory effect, proteolytic enzymes became of real clinical importance only when the American firms of Armour Pharmaceutical Company and National Drug Company began to isolate and produce them in pure form in the early 1950's

Chymotrypsin is a proteolytic enzyme of the endopeptidase group It has a specific catalyzing effect by hydrolytic decomposition of certain peptid bonds, but in healthy tissue it is neutralized by the enzyme inhibitors which are normally present It is produced from bovine pancreas and consists of at least six different substances with a molecular weight ranging from 22,500 to 25,000 The alpha form was produced by Kunitz & Northrop in 1933

The nature of its action has not been clearly elucidated Menkin and Day conceived the structure of the connective tissue as a macromolecular network which by inflammation undergoes permeability changes The pores of the network are completely or partially blocked by macromolecular units, for instance fibrine components The effect of the chymotrypsin is considered proteolytic, mucolytic, digestive, anti edematous, anti phlogistic and hematoma-reducing

It eliminates the nutrient of the bacteria and by liquefaction of the thrombotic lumps it causes improved blood circulation, increased lymph resorption and finally a normalized oxygen supply to the tissue

As compared with trypsin which was produced for clinical use some years earlier, chymotrypsin has been described by several authors as less toxic but more active in proteolytic and anti-inflammatory respect Furthermore the substance has been used successfully as a mucolytic agent in chronic pulmonary diseases with viscous expectoration

In 1957 Auslander presented a report on treatment of 106 patients suffering from serous otitis media and described how he had combined paracentesis and Politzer treatment with injection of the enzyme preparation "parenzym" 83 9 % of the patients responded immediately to the treatment, whereas in 17 cases the author was compelled to perform paracentesis twice Auslander regarded "parenzym" — which is a trypsin preparation — as a useful adjuvant in treatment of serous otitis

Gessert et al (1960) studied the effect of various enzymes on the middle ear secretion in in vitro and in vivo trials and demonstrated among other things the mucolytic and proteolytic properties of trypsin and chymotrypsin The author used enterosoluble Chymar tablets — 1 tablet 3 times daily for 4—7 days — on a total of 10 patients Five of these patients also underwent paracentesis Four patients had subjective improvement, but only in one case did the secretion disappear completely from the middle ear However, the viscosity of the secretion seemed to diminish after the treatment The authors mention that injections with proteolytic enzymes direct into the tympanic cavity might be more effective, but on the other hand such treatment may involve a certain risk

Litton & McCabe (1962) studied the effect of water soluble alphachymotrypsin in in vitro-trials, and took secretion from both ears of 4 patients who were suffering from adhesive otitis After addition of Ringer's solution a suitable quantity of alphachymotrypsin was applied to 4 of the 8 test tubes After 15 minutes the mucos secretion became quite clear and aqueous in the test tubes

where the enzyme preparation had been added, whereas in the control test tubes this was not the case

The authors regarded local application in the tympanic cavity as a more effective administration form than universal treatment with enterosoluble tablets or intramuscular injections

In 31 cases of "glue ears" Chymar in water soluble form was injected into the tympanic cavity through the tympanic membrane The dose required was determined by the swelling of the membrane After a certain interval, which was not indicated paracentesis and aspiration was performed If necessary, adenoidectomy was performed The injection into the middle ear could be administered without difficulties to adult patients with our local anaesthesia Several patients declared that their hearing had improved already before paracentesis was performed and in the cases where there was no tubal occlusion the patients frequently declared spontaneously that they felt a flow of liquid into the throat The tympanic membrane was soon restored to its normal position and paracentesis could be avoided

The authors observed no side-effects in connection with the chymotrypsin treatment They concluded that in aqueous solution and in the above application form chymotrypsin has a solving effect on the viscous middle ear secretion

Own investigations

At the ear department of the University Hospital in Copenhagen the enzyme preparation Chymar has been used on a trial basis since the autumn of 1962 in various diseases, where edema hematoma or secretion retarded the healing Especially a series of trials has been carried out to determine the effect in rhinoplasty These studies — which it is our intention to publish in the Danish Medical Journal — show that the preparation has a reducing effect on edema and hematoma We particularly observed more rapid regression of the more severe traumatic manifestations especially around the eyes where the tissue is loosely connected

During the last 4 months a total of 25 patients from various age groups suffering from massive chronic adhesive otitis have been treated with Chymar Thirteen patients had previously been treated according to the conventional principles with no appreciable effect Fourteen patients were treated with Chymar tablets — 2 tablets 4 times daily for 6—12 days — or with the injection preparation in doses of 5000 Armour units twice daily for a similar period Seven of the patients underwent paracentesis parallel with the enzyme treatment and aspiration from the middle ear was performed Only in one case did the secretion disappear whereas the remaining patients had no certain subjective improvement

Twelve patients all of whom were suffering from "glue ears" had Chymar injected in water soluble form in a dose of approximately 2500 Armour units direct into the middle ear Before the injection paracentesis had been performed and as much as possible of the viscous secretion had been removed Nine of the patients had previously undergone repeated paracenteses as well as aspiration

and on an average such treatment had been given at intervals of 2—3 weeks without curative effect

In a total of 6 patients decreasing viscosity of the secretion was observed already at the second injection Two of the patients who were previously compelled to wear a hearing aid did not need it any longer In 4 of the 6 patients the intervals between the paracenteses could be extended to an average of 35 days because of subjectively improved hearing In the remaining 6 patients no certain viscosity changes could be observed, nor did the hearing improve beyond what had previously been observed by paracentesis and aspiration Two of these 6 patients had, however, in addition to the adhesive otitis suffered from vasomotor rhinitis which did not respond to antihistamine treatment Two other patients in this group had only received 2 Chymar injections and it was thus difficult to draw any conclusions

No allergic manifestations or other side effects were observed in the above series Especially, no case of reduced hearing or effect on the organ of equilibrium was observed

Application of enzyme preparations to the middle ear is of course reserved for treatment by specialists Our therapeutic experiments have been carried on for 4 months only At present it is therefore impossible to say anything about the actual effect and the above paper should therefore be regardet as a preliminary report In the cases observed by us Chymar has proved to have a dissolving effect on extremely viscous secretion Moreover, improved hearing has decreased the number of paracenteses and we find that this fact alone is enough to justify a continuation of the trials

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a tubotympanal one A fibrously healed mastoid causes no marked irritation and can be left undisturbed The surgical problems can be focussed on two main points, dissection of the drum from the promontory and its new epithelization, and on permanent ventilation of the middle ear

Dissection of the drum from the promontory can best be made utilizing incision which includes a good part of the ear canal skin Posterior tympanotomy is then performed, the drum loosened from the annulus and dissection carried forward The adhesions around the ossicles are removed and the mobility of the chain thus ensured

Further tympanic dissection can be made by two methods The method of

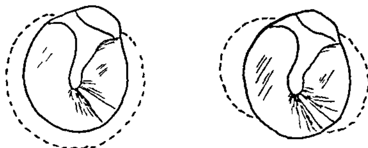


Fig 1 Two different incisions used to mobilize the drum on the left the incision mobilizes the whole pars tensa on the right anterior and posterior tympanotomy are made

Zollner consists in mobilization of the whole drum via a circumferential incision leaving the drum attached only at the area of Shrapnell's membrane An excellent visibility into the tympanic cavity and to the tubal orifice is obtained

Another method, which I have used more often, utilizes a combination of anterior and posterior tympanotomy It differs from Zollner's incision only in that it leaves the inferior attachment of the tympanic membrane intact, the drum being dissected free from the anterior and posterior direction and the tube approached through the anterior tympanotomy opening

If only one or two membraneous septa close the tympanic orifice of the tube, their removal generally results in good hearing These cases can as a rule be predicted before operation air is heard to enter by a tubal catheterization but no movement of the drum is seen

Generally the problem is much more difficult, the tubal lumen being full of granulation tissue The soft tissues should be removed cautiously with a fine curette or forceps working as far as the bony protection of the tubal walls perm its Dissection should not be done in the membraneous portion of the tube, even the bony canal may present dehiscences and the proximity of the carotid artery and its surrounding venous network should be kept in mind As recommended by Wullstein, tubal dissection should be discontinued if bleeding from the veins is encountered

Zollner obtained fairly good results with polyethylene tubes leading from the tympanic cavity to the nose, but my own experience has not been so favourable Therefore, if the tubal occlusion has been found to be extensive, I have re-

frained from further efforts and concentrated on creating a free access for air from the meatus to the tympanum

One possible way of effecting this is via the antral window as recommended by Zollner, because of the tendency to closure of and growth of skin into this window this route is no longer popular Another method is to make an opening in the drum and try to keep it open indefinitely, my experience is limited to this operative approach

I have arrived at the use of a polyethylene tube in adhesive tympanum after treating cases with secretory otitis by keeping a tube several months in the tympanum The difference is that in an adhesive middle ear the tube is intended to be left in the tympanum for life the drum undersurface is raw after tympanotomy and that no extra aeration of the tympanum can be counted on from the Eustachian tube

In cases with a large raw area in the drum undersurface a polyethylene tube was first introduced through the meatal incision the broader end lying anterior to the malleus handle After some weeks when epithelization had taken place, the tube was shifted to go through the drum proper In cases of adhesive middle ear the meatal tube very soon becomes blocked only a short tube placed direct through the drum has a chance to stay open and admit air to the tympanum

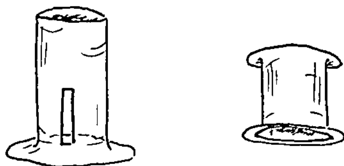


Fig 2 Two types of polyethylene tubes employed for permanent ventilation of tympanum from the meatus On the left the tube is 4 to 5 mm long and has three longitudinal cuts at the lower end to facilitate the air exchange The button on the right is employed in less severe cases

A special fashioning of the tube has been found necessary The tympanic end of the tube is made broad by heating and the lateral extension curled upwards to lift the drum from the promontory Further 2 or 3 longitudinal openings are cut into the tube allowing the air to enter through the upper surface of the drum direct into the tympanum without needing to traverse the end lying on promontory Another method is to insert a polyethylene button into the myringotomy opening

Sometimes it has been necessary to change the tube because it has become blocked or because it has slipped out of the ear Opening of the tube is often accomplished after instillation of α chymotrypsin into the ear under microscopic suction The tympanic membranes have tolerated the tube well without

reaction However, the opening has not become permanent even if the tube has been left in place over one year

Finally one case is described which has the longest observation period

The patient, 30 years of age, became hard of hearing during the first ten years of life non drained otitic infections resulted in totally fixed tympanic membranes with no sound of air or movements during tubal catheterization

During the last five years, the right ear was treated elsewhere by various means, including mastoidectomy, a modified radical operation with open cavity, and finally by stapedectomy

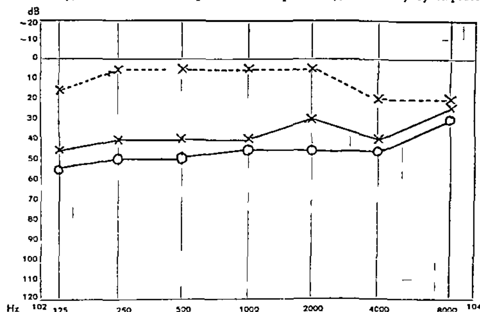


Fig 3 Audiogram of a case described in the text The right ear after several operations without permanent ventilation of the middle ear has a 50 db hearing level The interrupted line shows the result for the left ear after liberation of the drum from the promontory and insertion of a polyethylene tubing

with a polyethylene stapes placed over a fascial graft. Hearing improved for a week or two, viz until the drum became fixed again to the promontory

Liberation of the drum from promontory in the left ear was made on April 15, 1962 The Eustachian tube was full of fibrous and granulating material, and it was not possible to open it Therefore a 2 cm long tube was inserted through the meatal incision and allowed to lie under the malleus handle On removal of the dressing hearing was found to have risen to zero line but after four weeks the tube became blocked It was possible to open it several times by α chymotrypsin rinsing, but after eight weeks the tube was permanently blocked A new short tube with side entrances was then placed into the tympanum through the drum and hearing remained normal for the next 6 months The tube then became dislodged once and was re-inserted once it became blocked but opening succeeded with α chymotrypsin At other times hearing has been normal in this ear

It should be emphasized that after initial liberation of the drum, changing a polyethylene tube in the tympanum is a minor procedure which can be done easily as an office procedure with the aid of the operating microscope If the Eustachian tube cannot be opened, the method described seems to offer a reasonably well functioning alternative for aeration of the tympanum

SUMMARY

In fully developed adhesive middle ear, alleviation of conduction deafn can only be obtained by two means functioning of the Eustachian tube shou preferably be restored or if this is impossible, aeration of the tympanum accomplished from the meatus Aeration must be permanent, otherwise the l results will be poor owing to recurrence of adhesive tympanum Permanent ve tilation of the middle ear has been achieved with the aid of a special polyeth lene tube or button passed through the drum and allowing entrance of air

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SOME PROBLEMS CONCERNING THE PROGNOSIS AND TREATMENT OF ADHESIVE AND SECRETORY OTITIS

By

Jorgen Arnvig

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Abstract

Three questions to the lectures

Does with adhesive otitis the mastoid usually appear as a badly pneumatized structure?

After a meato-antromia closure of the operatively opened aditus often takes place

Can by this operation a more constantly functioning air hole be provided for?

Will in cases of badly pneumatized mastoids the ordinary X ray treatment of the Eustachian tubes possibly increase the stenosis?

At the Scandinavian congress of otolaryngology in Helsingfors 1960 Surala proposed to make a meatoantrostomy in those cases of adhesive otitis where a normal function of the Eustachian tube could not be obtained By this operation the aditus ad antrum was opened to function as an air hole for the middle ear thus replacing the blocked tube and securing normal hearing

At the ENT department of the state hospital in Sonderborg a meatoantrostomy was performed in four cases of dysfunction of the Eustachian tube As these cases are of general interest too a brief report and a discussion is given below

The patients were children of ages between 12 and 15 years and had for several years suffered from adhesive otitis This is not the place to go into details as regards the results of the different examinations and treatments, only it is to be mentioned that two of the patients got deep x ray treatment of the Eustachian tubes with low dosages of 300 and 375 r respectively without any effect

A meatoantrostomy was performed on all affected ears The pneumatisation of the four mastoids was very bad as previously seen on the roentgenograms, which showed a completely normal pneumatisation on the healthy ears In the mastoid bones operated on only a very few cells remained with a thickened mucosa and a mucous excretion being black, dark brown and in one case yellowish In all cases a viscous exsudate was found in the antrum, the mucosa here being either normal or slightly thickened

Microscopy of the mucosa was performed in two cases showing a normal cubical epithelium and a stroma being rich in cells with no signs of inflammation

Postoperatively a dry cavity was obtained in all cases The operatively opened aditus for the first patient did not close until one year and a half later, the hearing being normal throughout this time In the other cases the fistula closed after some months

SUMMARY

In fully developed adhesive middle ear, alleviation of conduction deafness can only be obtained by two means functioning of the Eustachian tube should preferably be restored or if this is impossible, aeration of the tympanum is accomplished from the meatus Aeration must be permanent, otherwise the late results will be poor owing to recurrence of adhesive tympanum Permanent ventilation of the middle ear has been achieved with the aid of a special polyethylene tube or button passed through the drum and allowing entrance of air

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DISCUSSION

Berdal to Buch and Kristensen

At the E N T department, Rikshospitalet, Oslo, we have used chymotrypsin in a few cases of secretory otitis media, and it appears to have a beneficial effect In particular I will mention 3 cases of bilateral otitis of long duration with symmetrical otoscopic findings and identical *conductive hearing loss on the two sides* These patients, all children between 5 and 10 years, were treated with unilateral paracentesis and aspiration of thesecretion, followed by daily inflations ad modum Politzer Chymoral[1] was given at a doze of one tabl 3—4 times a day In all cases the ears cleared up, and normal hearing was obtained in the course of 8—12 days The improvement appeared rather quicker in the ears in which paracentesis was not performed. The medication of Chymoral and inflations were continued for 3—4 days after the symptoms had disappeared and the hearing had returned to normal. It is of course impossible to judge definitely the effect of Chymoral, but we have found the results of this treatment *encouraging* We have planned to continue the investigation

Holmgren to Ingelstedt

Among all the interesting lectures and beautiful curves, my attention was quite especially drawn to a picture in S Ingelstedt s analysis It showed a mound and a coffin deep down in the earth, and it could have had the heading Here rests the Hearing'

Our finest methods of treatment will be of no use whatsoever if we do not examine the children while the substance in cavum is still liquid and can be emptied and before the process has advanced too far The following program must be carried out and has proved to be surprisingly successful if everybody cooperates

1 Information to parents, teachers, and authorities granting funds

2 Mass screening of all school children in the first class to start with, and examination of every pupil who has trouble with the ears or — just as important — does not get on so well at school I can report that hearing tests by play audiometry are at present carried out on all 4 year old children in the county of Norrbotten, Sweden, organized by the Chief M O of the Boden Hospital, Gunnar Holmgren

3 All children with diagnosed hearing defects must absolutely be taken care of for treatment 'It is wrong not to examine the hearing of children, but what is still worse is not to treat a recognized hearing impairment"

4 Checks ups of the above program

Ingelstedt s picture was crowned by a beautifully decorated mound It symbolizes all the beautiful phrases and intensions that did not come to anything I think Let us all, you and I, when we arrive home from this extremely interesting congress, take a spade and start digging And when we open the grave we will find that the hearing lives — it has only been seemingly dead

Fabritius

It is not surprising that the definition of the different forms of inflammation in the ear gives rise to difficulties, because if one observes children with these diseases — in the way in which it is possible through systematic school child examinations, one will find that there is a gradual transition from catarrhal to purulent ear diseases and from the acute to chronic forms of these

From that which has been said earlier to-day about the diagnosis "adhesive otitis" it is clear

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[1] One tabl Chymoral equals 50 000 Armour units pancreatic enzym (Trypsin and Chymotrypsin 6 1)

that this is a but poorly defined notion In the clinic, that on which one must rely, is the appearance of the ear drum the hearing function and the anamnesis

Not infrequently one finds the hearing of a school child to be normal when one on a previous occasion had found a considerably impaired hearing — and where one from the clinical picture had made the diagnosis "adhesive otitis" The diagnosis is therefore, in my opinion, not to be made spontaneously, but only after a longer period of observation — and on anamnesic grounds Such anamnesic material can be difficult enough to acquire from those of school age, and it is equally difficult to throw light on the subject amongst those of greater age, because people so seldom know what happened to their ears when they themselves were small ones One can hardly make a diagnosis of adhesive otitis unless the hearing is considerably impaired

In order to give a better idea of the frequency of adhesive otitis in a school child material, I can mention that amongst 6,000 school children whom I observed throughout all their seven school years, I found only five that seemed to qualify for this diagnosis Amongst these, however, there were three who had had numerous otitises earlier, and these ought therefore rightly to be put into the group headed 'recidua'

There were therefore only two who had chronic catarrhal otitis which developed into that which one should classify as adhesive otitis The one developed between the 1st and 4th class the other between the 4th and 7th class Neither of them had had otitis, and the reason for the development of the adhesive otitis picture could not be found In both an impairment of hearing between 35 and 40 db occurred on the affected side

That which is of the greatest interest is the prophylactic precautions which should be taken With regard to constantly relapsing otitises the case is comparitively easy, namely treatment as early and as thoroughly as possible

As for relapsing otosalpingitis which proceeds to adhesive otitis the case is somewhat more problematic because one lacks aetiological backing The total of 2 amongst 6 000 shows that this is not a pressing problem, but it is serious enough on account of the deafness which results — and it is undoubtedly a problem that is awaiting its solution

Falbe-Hansen to Arnvig

Referring to Arnvig s question whether treatment with radiation may possibly provoke stenosis of the Eustachian tube, I can state, that I never have seen it, in spite of many years' experience with X ray as well as with radium treatment Theoretically it should be impossible to get damages with an X ray dose of 200—300 r The radiation dose from treatment with radium is a little larger, but on the other hand, the field is much smaller I prefer treatment with radium in childhood and with X ray in adults The results are encouraging The beneficial effects persists for only a couple of years but in children this period of time very often means that they reach an age group when the normal regression in lymphoid tissue assists in minimizing the effects of stenosis of the Eustachian tube

Falbe Hansen to Ewertsen

I will most strongly warn against giving a hearing aid to a child with a conductiv hearing deficit and then failing to follow the child closely in short intervals Through this procedure there might be a risk in missing a progressive deafness where the progression might have been arrested by proper treatment It is imperative that the hearing centers send these children for treatment to their local otologist or to a special department of otorhinolaryngology

Diamant to Ingelstedt

I take the opportunity to greet to day s lecturers on the theme of tubal function and its implication for the development of serous otitis media I congratulate Dr Ingelstedt to his genious methods for measuring the volume of the mastoid air cell system I greatly appreciate that he has accepted the terms small and large" when speaking in general of size of air

cell system instead of the inadequate terms "inhibited" and "normal" The terms 'small" and 'large" in this connection unprejudicedly refer to what we actually are classifying in this way, whilst 'inhibited" and "normal' represent what we, most probably falsely, conclude concerning interference with development of the air cell system In this connection it may again be stressed that references to Wittmaack are just as inadequate Wittmaack's investigations have in fact no bearing with size of the air cell system as he himself repeatedly has maintained.

Dr Arnvig in his lecture inquired concerning our knowledge on extent of pneumatization as related to cases of serous otitis media May I remind of an article in Acta oto-laryngologica (volume 49) published by me together with Rubensohn and Walander In our investigation on this matter we could show that serous otitis media preferably affects ears with a relatively small air cell system as compared with the distribution of the various sizes in the population

According to my investigations in 1940, later confirmed by other investigators, the mastoid air cell system in the adult population shows a variation in size from 0 cm² to about 30 cm² when measured with a planimeter on the X ray picture in lateral projection I do not think it necessary again to stress that I have repeatedly stated that the planimeter measuring does not give the volume of the air cell system, though I have shown a strong correlation between the size measured on the X ray picture in the lateral and in the frontal projection. According to investigations by Dahlberg and me in 1945 the final size is predominantly inherited, whilst non pathological environmental factors exert a relatively minor influence

My investigations in 1940 also show that all kinds of otitis have a tendency to affect ears with small air system, though to significantly different degrees Thus, no marginal perforation is found when the size exceeds 10 cm², no central perforation is found above 15 cm² and no acute otitis above 25 cm² Relative risk figures computed show that the risk increases with decreasing size of air cell system

Against this background I would like to ask Dr Ingelstedt as to whether in his investigations on volume of the air cell system in the group of so-called chronic otitis cases he has divided into cases with central and marginal perforation respectively By doing so I could show statistically significant differences concerning planimetric size between these two groups and personally I believe that they represent two quite different diseases

In his lecture Dr Ingelstedt also suggested that the drum membrane perforation may represent nature's own way to relase the situation of a closed tuba I believe that this cannot be the case As a matter of fact we have practically no possibility to create a permanent perforation in the drum membrane in cases of serous otitis media. Not even the using of a polyethylene tube for months seems to be able to prohibit the closure of the perforation after removal of the tube Furthermore, I have never seen a case of serous otitis media spontaneously causing a perforation of the drum membrane, not even in ears with very small air cell systems I conclude therefore that the creation of a central perforation in cases with small air cell systems must depend on factors not being present in the disease called serous otitis media, just as again another factor is needed in the creation of the marginal perforation of the drum membrane That would mean that we *have to face with 3 different diseases, namely cases of serous otitis,* cases with central perforation and cases with marginal perforation Whatsoever, we cannot serve relevant problems by investigation groups of chronic otitis" I therefore suggest that we abandon the use of the term as well as the grouping of chronic otitis" for once and for good

Garbne to Barr and Klockhoff

According to Barr & Klockhoff's paper read here, secretion from the middle ear through the polyethylene tube was a frequent phenomenon among the patients they treated I have been able to observe such secretion in exceptional cases only I wonder if this difference is attributable to the fact that mastoidectomy had been performed in the majority of the cases before the introduction of tube therapy, thereby removing the secret producing glandlike areas It is also possible that a different technique of aspirating the fluid from the middle ear may be the reason I made an effort to remove, by turning the patient's head repeatedly, all fluid from the middle ear and the cavities of the mastoid process

MYRINGOPLASTY USING SEPTUM CARTILAGE

By

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Abstract

Myringoplasty on 25 cases with subtotal eardrum perforation has been made with material from the foremost part of the nasal septum The transplantate consists of nasal cartilage without the nasal epithelium removed This tissue gives a stiff membrane resistent against necrosis with sufficient acoustical qualities 23 cases have healed without complications

Since Zollner and Wullstein began about 15 years ago in connection with tympano plastic reconstructions to a greater extent to replace a defective drum membrane with a full skin graft, our idea of the most suitable graft has varied a great deal

At first a retroauricular full skin graft was suggested (Wullstein, 1952, 1959), then the same thing stalked (Moritz, 1952, Zollner, 1952), then the skin of the auditory canal (Frenckner, 1955, Plester Nysten, 1959, Wastenson, 1961) but, after indications of subsequent complications in the form of cholesteatoma or deep cellulitis in the graft (Beickert, 1958, Schuknecht, 1960), skin as material has increasingly been replaced by other tissues With more or less success the use of amnion membrane (Schrimph, 1954), mucous membrane of the cheek (Hall, 1958), periosteum (Agazzi, 1960), fascia (Heermann, 1961), vein tissue (Shea 1061) and dura mater (Preobrazhensky, 1961) has been recommended

THE PROBLEM

In cases of smaller perforations most of the body's tissues can be used with safety but the task of the graft is here only to form an irritation of the remaining eardrum so that it is stimulated to healing in the same way as with etching by *nitrate of silver or trichloracetic acid* When the perforations are larger the situation is completely different Here the graft must replace the tissue of the drum membrane But which part of the drum membrane should one replace, the lamina propria or the thin epithelium layers on the inner and outer side? The most functionally important part of the eardrum is certainly the lamina propria (Secondi 1951), the collagen fibres' rich skeleton of connective tissue, on the inner and outer side of which the thin epithelium layers sit like wallpaper As these epithelium layers easily regenerate from the surrounding tissue, they are from the point of view of the graft only of secondary importance But the lamina propria does not recover so earsily It would therefore be logical to attempt to repair the perforated drum membrane with a tissue as similar as possible to lamina propria and then let the epithelium grow out from its environment and cover the healed and built up graft

This is the intention behind the use of connective tissue, periosteum, fascia, vessel tissue and dura mater These all belong, as does the lamina propria, to the collagen rich supporting tissues They are close to one another histologically and phylogenetically and ought therefore to be able to be used for grafting the eardrum

The connecting tissues named above have, however, certain disadvantages as graft material They are more or less soft, so that they easily sink in towards the promontorium with a risk of formining adherence The tendency towards coalescence between the graft and the wall of the tympanic cavity is increased by the fact that most of the materials turn a surface without epithelium to the middle ear A further unsuitability is the tendency to retraction shown by several of these tissues The graft shrinks strongly and thickens On account of this the use of conjunctive is stated to be impossible (Wullstein 1960) Finally, many of the grafts of connective tissue type are sensitive to circulatory disturbance If the eardrum perforation is too big the early unsatisfactory blood support will often lead to central necrosis, and because of this a vein graft is considered unsuitable for perforations greater than 25 % of the drum membrane's total surface (Schuknecht 1962)

METHOD

On account of these factors a different graft is desirable a firm, collagen rich connective tissue, which maintains its shape, is resistent to necrosis and is covered on one side with a flat non secretory epithelium

For more than a year the author has, to close larger perforations in the eardrum used a material which satisfies these requirements The tissue which has proved suitable is taken from the cartilaginous part of the septum nasi, within an area of about 15 mm breadth immediately inside the nostril The cartilage in this part of the septum is hyalin and surrounded by a well developed collagen rich perichondrium The cartilage is nutriated from the perichondrium by diffusion As the septum is positioned between two air-filled cavities, the blood vessel supporting the mocous membrane and perichondrium will run everyhere parallel and in these tissues The mucous membrane in the relevant area of the septum is composed of layered flat epithelium of the same kind as is seen in the cornea and on the conjunctiva In this area glands are almost completely absent and the area is also in practice secretorally inactive (Fig 1)

The rough untrimmed graft consists accordingly of a layer of cartilage, a perichondrium and a slice of layered unsecretory flat epithelium The epithelium makes a good connection with the flat or cubic epithelium of the middle ear and hinders subsequent adherences in the tympanic cavity The perichondrium, containing the all important connective tissue cells, numerous collagen fibres is the future drum membrane's final supporting frame The layer of cartilage is the most important part during the often month long reconstruction period It gives the graft an essential stiffness and stability of share as well as a clearly increased resistance to central necrosis The cartilage has in fact a low metabolism and is not dependent on vessel bound circulation, but helpfully achieves its nutrition

F g 1 Upper p cture Photomicrograph showing mucous membrane from the vest bular region of the nasal septum The epithelium of the mucous membrane is layered flat ep thelium Below this s seen the submucous area with collagen fibres but without glands van G eson stain Lower p cture as a comparison is seen photomicrograph showing the mucous membrane from the resp ratory sphere of the nasal septum The cylinder shaped ep thelium cells are here ciliated In the submucous area there are a multitude of glands van Gieson stain

by diffusion from its surroundings. The relatively resistent cartilage plate will therefore from the outside cover and protect the more vulnerable parts of the graft. Subsequent early necrosis central in the perichondrium or mucous membrane can therefore be repaired by the organism itself before the covering collagen cartilage is broken up and fused with the perichondrial tissue and with epithelium of the auditory canal.

TECHNIQUE

The method of procedure in the removal of the graft from the septum, its trimming and the final application to the region of the eardrum are most easily illustrated by the diagrams given below (Figs. 2—5).

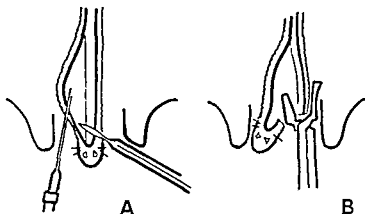


Fig. 2.

A. By local anaesthesia the perichondrium mucous membrane is loosened on one side from the underlying septum cartilage. From the opposite side a bow shaped incision is made through the mucous membrane, perichondrium and cartilage.

B. The inner cutting leg of a pair of tonsil tongs of the Leuwer pattern is introduced through the opening made by the incision as shown in the diagram. The size of tongs varies according to the size of eardrum in the intended operative case. In operations on adult patients tongs in which the inner cutting cylinder has a diameter of 12—15 mm are usually employed. This size of graft should be sufficient in most cases as the average drum membrane's maximum diameter is 10 mm (Brenninghoff—Goerttler 1960).

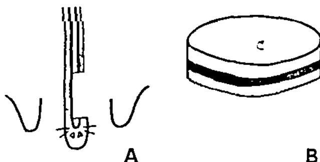


Fig. 3.

A. After the graft has been removed the septum in this area consists only of one intact mucous membrane perichondrium layer.

B. The rough graft is coin-shaped and consists of mucous membrane (the lower light coloured layer), perichondrium (the black area) and cartilage (the upper light-coloured layer).

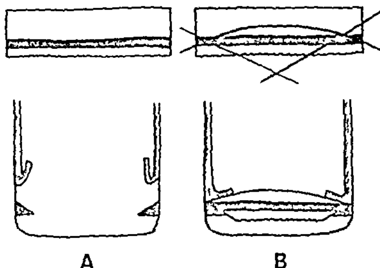


Fig 4

A Upper picture untrimmed graft Lower picture subtotal perforation of the eardrum The remaining drum membrane tissue has had the epithelium removed and the edges have been cut away The skin of the auditory canal has been loosened at the limbus by circumcision and let fall outwards

B Upper picture the untrimmed graft in a grown person is ca 12 mm in diameter When it is trimmed the cartilage is shaped so that only a slightly arched plate remains The maximum height of this is usually 0 5—1 mm The underlying perichondrium and mucous membrane is cut so that the rough surface is met at the periphery of the epithelialised side of the graft Lower picture the prepared graft has been put into place with the cartilage facing outwards and the mucous membrane against the tympanic cavity Between these the perichondrium is situated with a roughened surface at the periphery against the limbus and the remainder of the eardrum from which the epithelium is removed The skin of the auditory canal nearest the graft has been dropped down over the edges of the graft

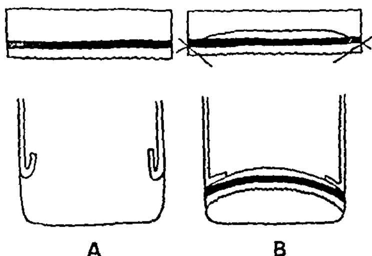


Fig 5

A Upper picture untrimmed graft Lower picture total perforation of the eardrum The skin of the auditory canal loosened at the limbus and let fall outwards

B Upper picture in an adult the graft should be about 15 mm in diameter When it is trimmed the cartilage is cut as in the preceding case (Fig 4) but is given a smaller cross cut than the underlying perichondrium The latter is cut so that the rough unepithelialised surface will be

turned towards the graft's cartilage side while the surface of the mucous membrane is left almost intact

Lower picture the graft has been put in place with the cartilage facing outwards and the mucous membrane against the tympanic cavity To obtain the desired volume of tympanic cavity the edges of the graft are pressed into the *sulcus tympanicus* On account of the natural tension in the cartilage plate the peripheral parts of the graft's outer side, i e the roughened perichondrium, will be pressed against the limbus area. The innermost parts of the skin of the auditory canal have, after application of the graft, been dropped back to cover the edges of the graft

After the graft has been loosened from the septum the relevant part or the nose is packed, and the pack has been removed the day after the operation

In the audiotory canal the graft has been held in place by fom rubber packs These have been removed after a week

RESULT

25 patients with total or subtotal perforations of the eardrum have been operated on with cartilage mucous membrane grafts In several cases (18) the ossicular chain has been intact (plastic type I) In some cases (7) only the stapes has been functionally capable (plastic type III) In 23 cases the graft has healed and the perforation has been sealed without any complications In two cases the graft has shown after operation a small dry central perforation The average improvement of hearing has for type I been 16 db and for type III 20 db An account of the other results is seen in Fig 6

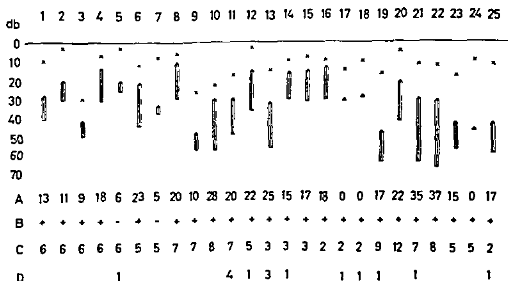


Fig 6 Preoperative bone conduction $\left(\frac{500 + 1000 + 2000}{3}\right)$ — × Preoperative air conduction $\left(\frac{500 + 1000 + 2000}{3}\right)$ = Ш Postoperative air conduction $\left(\frac{500 + 1000 + 2000}{3}\right)$ = ⊓ Improvement of hearing in db = A Eardrum perforation healed (+) or remaining (—) = B Observation time in months = C Number of earlier operative attempts = D Cases no 5 and

no 7 are not healed Cases no 5 and no 23 have got a smaller postoperative perforation of the nasal septum Cases no 17 and no 18 have had an earlier skin graft operation with a good postoperative hearing Case no 17 however suppurated as a consequence of a small perforation Case no 18 had an intact graft for two years but was troubled by a recurrent myringitis In both these cases the skin graft was cut away and the total perforation covered with cartilage perichondrium graft Cases no 1—18 = tympanoplasty type I Cases no 19—25 = tympanoplasty type III

DISCUSSION

Septum tissue has on 25 occasions been used as material for graft to seal total or subtotal defects of the eardrum and in 23 cases the result has been successful The patients were not specially chosen but represent occasional cases of large perforations treated at the clinic On 10 of the 25 patients there have been one or more previous unsuccessful attempts to close the perforation by skin or mucous membrane grafts

From the functional point of view one would suppose that a cartilage mucous membrane graft with relatively large mass and evident stiffness would give an audiogram with the best hearing in the low tone and high tone area but a poor hearing in the middle frequencies, i e one would get two areas of resonance instead of the normal single one at the frequency of 1000 cps Increase of mass shifts the resonance to the left with a lowering of the threshold for lower frequencies while on the other hand increase of stiffness shifts the resonance to the right giving a reduced threshold for high tones (Kobrak 1959) If these two factors (increased mass and stiffness) are combined, the audiogram ought, after plastic surgery of the eardrum with septum cartilage, to show the greatest loss of hearing within the areas of frequency where natural resonance has been situated and the best hearing in the new resonance areas in the descant and bass Audiograms taken early after the operation show in many cases similar curves with the least improvement of hearing at about 1000 cps This disappears, however, after 2—3 weeks and subsequent improvement in hearing is to a great degree similarly expressed through the whole range of the audiogram This can conceivably be interpreted as evidence of the graft s development, i e as a lessening of the mass and stiffness in that the cartilage plate disappears and is replaced by collagen connective tissue (Fig 7)

When skin is used for myringoplasty there always ought to be a postoperative air bone gap of 15 db on account of the skin's small structural similarity to the natural eardrum (Wullstein 1959) When septum cartilage is used, there is possible with a postoperative air conduction in immediate connection to the bone conduction This should indicate better acoustic qualities in the ready built up cartilage mucous membrane graft than in the graft of skin

This corresponds to the fact that the transmission is increased by tympanic membrane vibrating as a rigid cone even though such attachment increases the impedance of the tympanic membrane (Onchi 1961)

From a grafting point of view it may seem somewhat risky to involve perichondrium and cartilage tissue in a drum membrane graft The risk would be

that *the whole graft is transformed into cartilage* Microscopic postoperative studies of the septum graft have not, however, given any support for such fears About ten days after operation one finds that the originally yellow-white cartilage has taken *a dark grey blue colour. At the same time the moisture in the* cartilage has markedly increased All this is surely evidence of degenerative changes in the cartilage in which the chondromucoid dissolves and the collagen unmasks These changes are evident during the third to the fifth weeks They disappear first in the periphery of the graft and last in the central parts In the

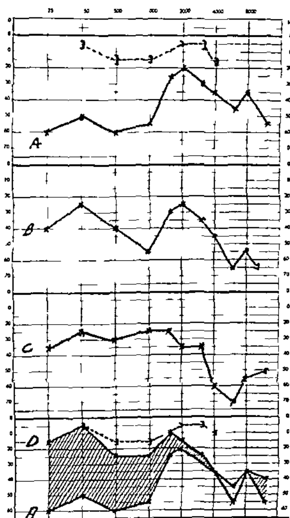


Fig 7 Case no 6 in the above account of results A Preoperative bone and air conduction Best hearing in the area between 1500—3000 cps B Air conduction 7 days after operation No improvement of hearing at the frequency 1000 cps C Air conduction 18 days after operation The improvement of hearing is similarly expressed through the audiogram D Bone- and air conduction 6 months after operation The shaded area indicates the improvement of hearing

periphery, in fact, the cartilage begins to dry after about 14 days and takes on a faint pink colour. Thin epithelium with fine vessels begin to be seen on the edges against the skin of the auditory canal. This building-up and development of epithelium continues without ceasing so that after 4—6 weeks the graft is soft and covered with a very thin, dry, shining epithelium. In this fine blood vessels are easily evident if the tissue is irritated e. g. by touching (Fig. 8).

As myringo-plastic surgery using septum cartilage is not especially difficult it can with advantage be employed in cases of total or subtotal perforation of the eardrum.



Fig 8 Healed and reconstructed cartilage graft covered with thin, dry and shining epithelium Note the fine vessels coming from the periphery of the graft

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CYTOARCHITECTURE OF THE ORGAN OF CORTI

By

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Abstract

The author has used special preparation techniques and phase contrast microscopy for the study of the normal and the pathologically changed cochlea of guinea pigs and squirrel monkeys A short description of this technique of making surface preparations of the organ of Corti will be given, as well as a presentation of figures showing the outstanding way in which it permits in one specimen the analysis of damage in every single one of more than a thousand consecutive sensory cells The surface preparation has replaced the preparation techniques earlier used by the author for several purposes and is characterized by its simplicity and reliability

A method is described by which surface preparations can be made of different portions of the inner ear epithelia It is possible to study these specimens with phase contrast microscopy, and by means of "optical sectioning" focus on different levels in the surface preparations By combining this method with micro dissection and plastic embedding plus phase contrast examination, an excellent concept can be obtained of the cytoarchitecture of the organ of Corti or of the vestibular sensory epithelia

During the past decade electron miroscopic studies have disclosed the fine structure of the various types of cells of the inner ear sensory end organs It is now becoming possible to detect the intracellular changes that underlie hearing loss caused by such damaging factors as intense sound, ototoxic drugs, circulatory disturbance and aging It would be the work of many years, however, to survey with the electron microscope the patterns of pathological change throughout the cochlea or vestibular system in order to relate these patterns to the functional disurbances Light microscopic study of the ear, on the other hand, by the standard celloidin method of preparation, is not only time consuming but unsatisfactory as well, since shrinkage and distortion during fixation, decalcification and embedding obscure the details of cellular structure Furthermore, in the usual mid modiolar sections one can see only a few cells at a time It is therefore customary to reconstruct the organ of Corti from examination of every tenth serial section, (Guild, Schuknecht) making the assumption, not always justified, that the cells in the intervening sections are in the same conditions as those observed

A method developed during the past year using "surface preparations makes it possible to examine the entire organ of Corti quickly and easily within a few hours after the specimen is taken from the animal and to plot the complete pattern of pathological changes that may be present Our surface preparations

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resemble the stained specimens studied by Retzius (1884) and by Held (1920), as well as the "Hautchenpraparate" as revived by Neubert (1952) and used by Beck (1959) and Vinnikov and Titova (1961) Our specimens, however, are either not fixed at all or fixed in a buffered solution of osmium tetroxide, in either case without further staining Large portions of the organ Corti can be examined by phase-contrast microscopy, and regions of especial interest can be embedded for further study under the electron microscope Thick sections of such embedded specimens can be cut by hand or with the ordinary microtome for light or electron microscopy When sections are required to follow a curved surface, as in the spiral ganglion or in a macula or crista, we often cut them by hand, using a specially honed razor blade

PROCEDURE

The inner ear structures can be studied without any previous fixation In this case the surrounding bone is taken away, the required portions of the sensory epithelia are dissected out and placed in a suitable mounting medium, and the specimens are examined under the phase contrast microscope

It is usually much better first to apply a suitable fixation fluid as this makes it easier to recognize the different parts of the inner ear For the study of the cochlea the top of the bony shell is lifted off and, the round and oval windows opened at the base Then a solution of 1 5 % cold veronal buffered osmium tetroxide is instilled A very good preservation of the cochlear structures can be achieved if the fluid is dripped on the top of the opened cochlea and then permitted to flow through the cochlea, leaving by the round and oval windows The specimen is then immersed in the fixation fluid and left for two hours in the refrigerator During this time the osmium tetroxide solution must be changed several times After 2 hours the specimen is thoroughly washed in physiological saline solution Under a dissecting microscope the bony shell of the cochlea and the underlying spiral ligament are removed Portions of the organ of Corti are then taken systematically, usually beginning at the apex These bits of tissue, representing one third to one-half turn each, are placed on numbered glass slides in a mounting medium of appropriate index of refraction (e g Zeiss Einschlussmittel W 15 or L 15 or glycerine) They are then examined by phase-contrast illumination, using magnifications of 100X to 1000X In a single preparation it is possible to examine as many as 1000 hair cells with their surrounding supporting cells, forming a regular mosaic pattern The method permits an analysis of the relations of the individual cells to one another and can reveal damage or loss even of a single sensory cell By focussing up and down one can by "optical sectioning" as it were, examine a series of horizontal sections through the organ of Corti studying and photographing for example, first the sensory hairs, then the reticular membrane and cuticular plates, the subcuticular mitochondria and basal body (Flock et al, 1962, Engstrom et al, 1962) of each hair cell, the nuclei, the nerve endings the supporting cells, and finally the basilar membrane and its blood vessels The condition of each cell is noted and the pattern of pathological changes can be plotted The cells in the various turns and

rows can be numbered and thus a complete and accurate record can be obtained of the condition of the entire organ of Corti

In accompanying illustrations we have tried to show how well the method

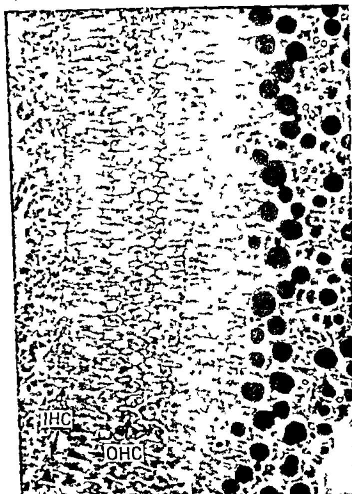


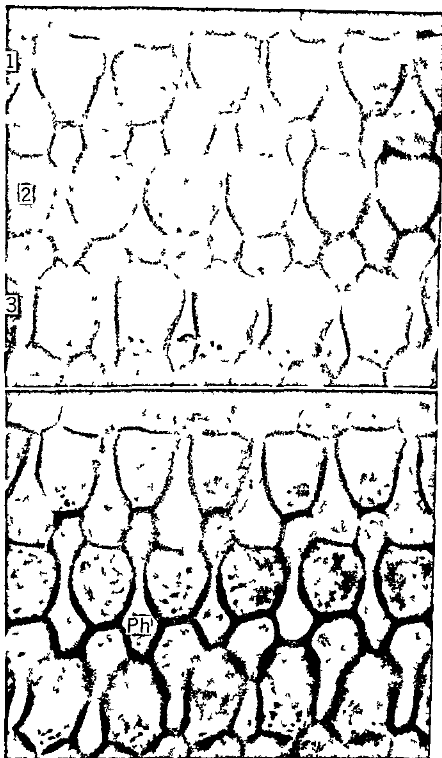
Fig 1 Low power phase contrast picture of the organ of Corti from a guinea pig showing the general arrangement of the cells IHC inner hair cells OHC = outer hair cells

permits an analysis of the cochlear cytoarchitecture In figure 1 the pattern of cellular arrangement of the organ of Corti can be readily seen, and the figures 2—5 also demonstrate the cytoarchitecture as seen at different levels in un sectioned material In figure 7, four cells dissected from the organ of Corti are shown Figure 8 represents a thick section from cochlea embedded in epoxy resin From this section the study can be continued by making further ultrathin sections for electron microscopy

The figures represent three different ways of examinig the organ of Corti In the following paper an application of the method of surface preparation to a pathological problem is described

A more extensive report of the method and its application to the study of normal and pathological cochlear cytoarchitecture is in preparation

This study has been made under contract N 6 2558—2631 US Navy



F g 2 The upper and the lower f gure are both from the same reg on of a m ddle cochlear co l from a gu nea p g and t shows how it is poss ble to focus at d fferent levels in the same specimen The upper f gure is opt cally sect oned through the cut cular reg on P = p llars Ph = upper phalanx 1 2 and 3 = three rows of outer ha r cells

Fig 3 Surface preparation through the organ of Corti of a guinea pig showing the arrangement of the hairs (H) at the surface The lower H indicate hairs in inner hair cells

Fig 4 Three rows of outer hair cells from a middle cochlear coil where the optical plane is deeper down in the cell than in fig 2

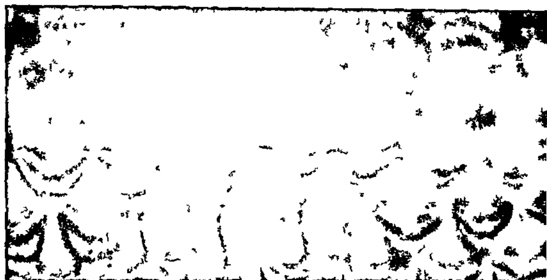


Fig. 5 Surface preparation from the basal coil of a guinea pig cochlea. Observe the great difference in the form of the cuticular plates and the arrangement of the hairs in this specimen when compared with figure [illegible] from a middle coil.

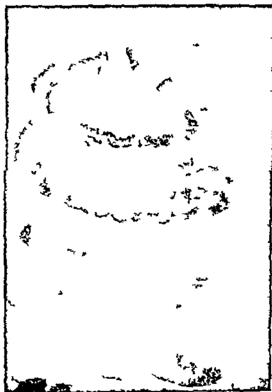


Fig. 6 *Upper part of a guinea pig* cochlea prepared so that demanded portions may be taken out for surface preparations. The black ribbon is formed by osmiophilic lipid-like granules inside the Hensen cell.



Γg 3 Surface preparat on through the organ of Corti of a gu n a p g show ng the arrangement of the ha rs (H) at the surface The lower H nd cates ha rs on nner ha r cells

Γg 4 Three rows of outer ha r ells from a m ddle cochlear co l where the opt cal plane is deepe down n the cells than n f g 2

The method of surface preparations, described in the previous paper (Engstrom, Ades and Hawkins, 1963) makes it possible to survey the cytological changes throughout the cochlea of a guinea pig within a day or two after the death of the animal From the surface preparations, each containing several hundred sensory cells in orderly arrangement, the pattern of damage can immediately be seen and recorded, and no graphic reconstruction is needed Many cytological details which are impossible to study in celloidin sections because of distortion and shrinkage are clearly revealed in surface preparations viewed by phase contrast microscopy As pointed out in the previous paper, the same specimen can be used for microdissection and, after plastic embedding, for higher resolution studies with the electron microscope It is often most appropriate to use one inner ear for surface preparations and to embed the other in epoxy resin Once can then cut thick sections for phase contrast or ultrathin sections for electron microscopy

The material used in the present study consisted of 11 guinea pigs weighing 250—300 grams Only those with active Preyer reflexes in response to the highest frequencies of the Galton whistle were chosen In addition to the large number of normal guinea pigs already studied by the method of surface preparation, two animals of the present group served as normal controls The other nine were given daily injections of kanamycin solution subcutaneously In seven animals the daily dose was 400 mg kanamycin base per kg body weight for 3, 5, 6, 7, 7, 8 and 9 days respectively One animal received 200 mg/kg daily for 10 days, and one 800 mg/kg daily for 6 days Each day they were tested with the Galton whistle The first animals were sacrificed when the Preyer reflex had just begun to fail, and the others in a consecutive series thereafter

The results of the kanamycin administration depended, as might be expected, upon the duration of treatment and the size of the dose Among the earliest changes to be observed was a distortion of the normal W pattern of the stereocilia on the outer hair cells So far as we are aware, this type of change, which is very striking in our preparations (Fig 1), has not been seen before, presumably because it can not be visualized with the techniques used in earlier studies The disorder of the hairs can be of many different degrees, from a slight irregularity to a complete disappearance of any pattern of arrangement As can be seen in Fig 1, there is no systematic change, and neighbouring cells can show different grades and forms of disarray At this stage shrunken or swollen nuclei can occasionally be seen, but they are not a constant finding

With increasing damage the hairs of some cells are entirely lost, and the whole cell may disappear, leaving an empty framework belonging to the reticular membrane (Figs 2, 3) Such losses involving single cells or several adjacent cells are easily recognized so long as the general cytoarchitecture remains It is then possible to count the number of cells missing in each of the three rows and thus get a very accurate estimate of the degree of the pathological change

The loss of cells can easily be tallied with 0's and •'s shown in the simple typewritten diagram reproduced in Fig 4

Where the destruction is severe, especially in the basal turn, even the supporting framework disappears and the normal configuration of the organ of Corti

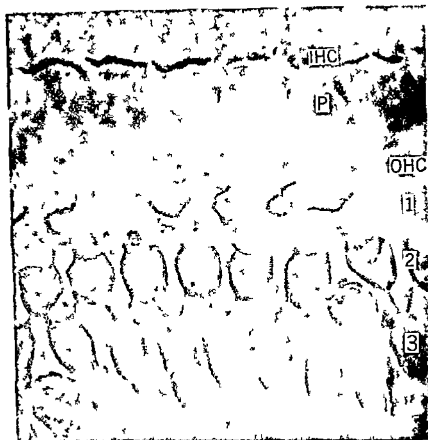


Fig 1 Distortion of W pattern of hairs on outer ha r cells of first row Two o h c are missing from row 1 Two extra cells are present between rows 2 and 3 and beyond row 3 Guinea p g SW 120 upper basal coil Kanamycin 200 mg/kg/day s c for 10 days

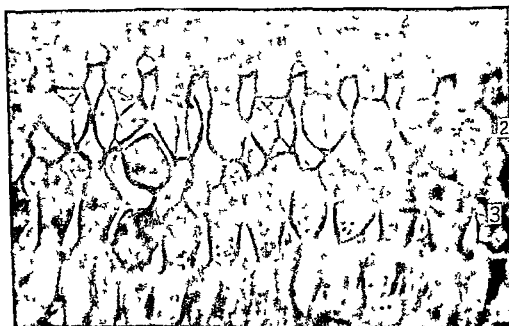


Fig 2 Loss of outer hair cells from row 2 Only empty ret cular framework rema ns in several cases Cells of row 1 not in focus but mostly destroyed Extra cell and cells of row 3 appear normal. Gu nea p g SW 125 upper basal coil Kanamycin 400 mg/kg/day s c for 8 days

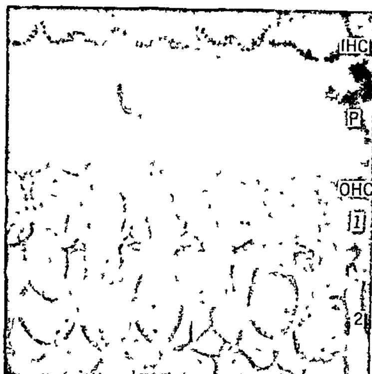


Fig 3 Typical hair pattern of inner hair cells Outer hair cells of row 1 and occasional cells in row 2 destroyed Guinea pig, SW 125 top coil Kanamycin 400 mg/kg day s c for 8 days.

is lost In such cases it is possible to specify the few cells that many remain, but not to state to which row they belong (Fig 5)

As has been shown by earlier light microscopic studies, (Hawkins, 1959, Ward and Fernandez, 1961, Darrouzet and De Lima Sobrinho, 1962), the inner hair cells are more resistant to the toxic action of kanamycin than the outer cells. Occasional inner hair cells may be missing, but no extensive destruction In the animal shown in Fig 3, a preparation taken ½ turn from the base of the cochlea had all outer hair cells missing in all three rows, whereas all the inner hair cells appeared normal

In general, the changes in the organ of Corti were most severe in the basal turn, as found also by light microscopy A second area of special vulnerability to kanamycin seems to be present in the third turn of the cochlea, whereas the second and fourth turns seem to be more resistant The first row of outer hair cells usually shows the greatest number of losses A rather typical distribution of missing cells can be seen in Fig 4

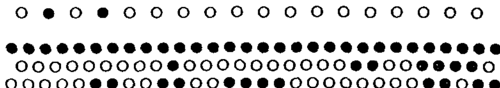
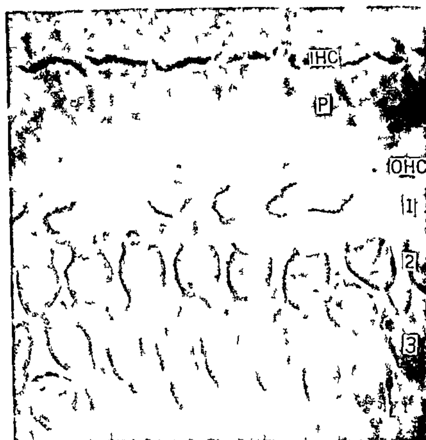
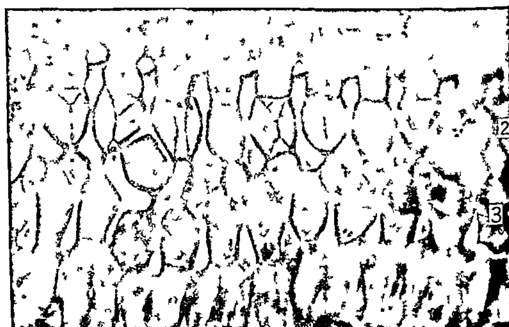


Fig 4 Diagram according to Engström, meant for computer use, showing distribution of hair-cell losses O intact cell filled O missing cell Guinea pig SW 120, 3rd coil Kanamycin 200 mg/kg/day s c for 10 days.



F g 1 D sto t on of W pattern of ha rs on outer ha r cells of f rst row Two o l c are m ss ng *from row 1 Two extra cells are present between rows 2 and 3 and beyond row 3* Gu nea p g SW 120 upper basal co l Kanamyc n 200 mg kg/day s c for 10 days



F g 2 Loss of outer hair cells from row 2 Only empty ret cular f amework rema ns n several *cases Cells of row 1 not in focus but mostly destroyed 'Extra cell and cells of row 3 appear* normal Gu nea p g SW 125 upper basal co l Kanamyc n 400 mg/kg day s c for 8 days



Fig 7 Loss of Claudius cells from upper basal coil Guinea pig SW 167 Kanamycin 400 mg/kg/day for 3 days

In this paper we shall not discuss any details of the intracellular changes in the hair cells These will be presented later in a report of the effect of kanamycin on the ultrastructure of the inner ear Nevertheless, one important feature of the inner hair cells should be mentioned That is the occurrence over considerable stretches, of a rounded, opaque clump near the nucleus of each cell We have tentatively called these 'paranuclear bodies' (Fig 6) Smaller agglomerations of similar type are sometimes seen in the outer hair cells

The supporting cells seem to be more resistant than the hair cells to the toxic effect of kanamycin Occasionally, however one or more pillar cells may disappear

In those animals which received the greater number of doses of kanamycin, considerable destruction was seen in the basal coil of the cochlea beyond the outermost row of outer hair cells This damage seemed to consist mainly in degeneration of the Claudius cells, leaving an irregular, granular-appearing network, as seen in Fig 7

The damage caused by kanamycin in the cochlea of the guinea pig is at first scattered, depending apparently upon the greater sensitivity of certain of the outer hair cells With continued administration of the drug, the destruction becomes localized, especially in the basal coil and, in our material, to a lesser extent in the third coil This suggests either a greater concentration of kanamycin in these regions or a higher vulnerability of these cells In general, our findings support the hypothesis that kanamycin interferes with metabolic processes that are essential for maintaing the normal cellular morphology and cytoarchitecture, as well as for the functional activity of the cells This interference could also be indirect, through damage to structures supplying oxygen or important metabolites

The striking difference in sensitivity between the inner and outer hair cells is

in good agreement with the great differences in structure between these two kinds of cells There is also a great difference in the relation to their surrounding structures There is even a possibility that their supply of oxygen and metabolites may be differently affected As we have often emphasized, the nutrition of the cells inside the organ of Corti is little understood This problem is clearly and intimately related to the problem of susceptibility to damage by toxic agents

Even among the outer hair cells there appear to be significant differences in sensitivity to kanamycin The cells of the first row are most vulnerable in the upper coils, whereas the cells of all three rows are easily damaged in the basal coil It is of interest to recall that in the upper part of the cochlea the cells of the first row have a smaller volume and a richer innervation than those of the second and third rows, whereas in the basal portion the cells of all three rows have a small volume and the same rich innervation (Smith and Sjostrand Eng strom, Ades and Hawkins)

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DISCUSSION

Flottorp to Hawkins

The very nice demonstration of selective destruction of hair cells by means of Kanamycin suggests that you with this drug and your histological method might be able to check one of the recruitment theories As you know it is assumed that in an ear with the outer haircells destroyed and the inner haircells still functioning, loudness recruitment will occur

By means of Kanamycin you should be able to destroy some portion of the outer haircells, but not the inner ones

Therefore, giving some animals adequate dosage of this drug, and then combining behavioural studies with your histological examination, one should certainly expect to obtain interesting results concerning the role of the inner and outer haircells in the mechanism of hearing

in good agreement with the great differences in structure between these two kinds of cells There is also a great difference in the relation to their surrounding structures There is even a possibility that their supply of oxygen and metabolites may be differently affected As we have often emphasized, the nutrition of the cells inside the organ of Corti is little understood This problem is clearly and intimately related to the problem of susceptibility to damage by toxic agents

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The distribution of pathological changes in the cochlea after administration of kanamycin has been described by several authors, especially Ward and Fernandez (1961) and Darrouzet and Sobrinoho (1962) on the basis of graphic reconstruction (Technique of Guild, 1931, and Schuknecht, 1953) The damage that they reported was for the most part similar to that which we have described The method of surface preparation, however, has the great advantage of revealing early and scattered changes in the hair cells, that are not seen by the other methods Thus the disarray of the W pattern on the hair cells in an early and *easily recognized effect of kanamycin, not revealed by the classical methods* The method of surface preparation is not only far simpler and far less time-consuming than the standard histological techniques but also more accurate and informative It should be extremely useful in the routine evaluation of the ototoxicity of new antibiotics related to streptomycin

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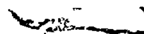
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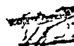
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HISTOCHEMICAL STUDIES ON GLYCOGEN IN THE COCHLEA OF DRUG-INJECTED GUINEA PIGS AND ALLOXAN DIABETIC WHITE RATS[1]

By

J Falbe-Hansen

From the Department of Otolaryngology, Kommunehospitalet Copenhagen

It was shown in a previous study (Falbe Hansen & Thomsen, 1963) that a PAS-positive substance, digested by diastase, occurs with great regularity in the outer hair cells of the organ of Corti in the normal guinea pig The substance must be assumed to be glycogen, it is present in the form of fine granules, and the outer hair cells in the apical turn of the organ of Corti are masked by these granules The amount of the substance decreases towards the base of the cochlea, where the hair cells are almost free from glycogen The inner hair cells are practically glycogen-free throughout all the turns of the cochlea The spiral ganglion shows varying amounts of glycogen grains from animal to animal, but here too there is a pronounced decrease in amount from apex to base No grains of glycogen have been demonstrated in the vestibular part of the labyrinth except in the ganglion cells

In the present paper, the studies of glycogen have been extended so as to include the white rat, and in addition, the guinea pig has been used to determine the effect of certain ototoxic pharmaca on the occurrence of glycogen Finally, a series of white rats have been made alloxan-diabetic, and the cochlea then examined for glycogen

The occurrence of glycogen in the cochlea of the normal white rat[2]

A total of ten normal, white, non-fasting rats, weight varying from 150 g to 240 g, average weight 165 g, were used for this investigation All the animals were in possession of their hearing (Preyer's reflex) and showed normal vestibular reactions

The animals were killed by decapitation under ether anaesthesia, the bulla opened, the stapes removed and the first turn of the cochlea opened in less than two minutes The labyrinths were fixed in ice cold 95 % alcohol, further procedure being as described by Falbe Hansen & Thomsen (1963) In the present

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[2] Both the normal and alloxan diabetic rats were made available by the kindness of Novo Therapeutic Laboratories Ltd Copenhagen

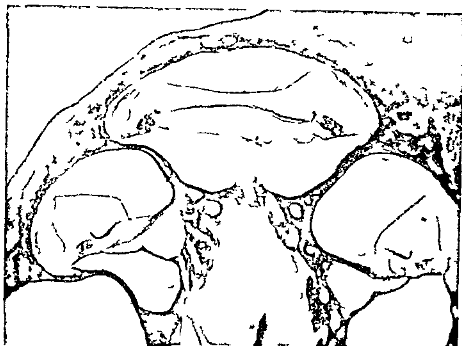


Fig 1 Normal white rat Top of cochlea PAS staining



Fig 2 Normal white rat Organ of Corti apical turn PAS-staining

studies however the procedure of drilling through the wall of the cochlea and making whole preparations was only rarely employed

The distribution of glycogen found in the sensory cells of the cochlea of the rat was the same as in the sensory cells of the guinea pig cochlea but in addition

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Experimental investigations

It is resonable to assume that the large amounts of glycogen found in the cochlea of a number of species of experimental animals represent a depot of fuel, to be employed under certain conditions, such as prolonged and severe acoustic stimuli However, experimental attempts to demonstrate this by applying such stimuli, have so far given negative results (Thomsen 1963)

A number of ototoxic pharmaca are known to damage the sensory cells, the supporting cells and the ganglion cells in the cochlea in fact those very cells which are often most rich in glycogen Histochemical studies were therefore made on poisoned cochlea, in the hope that by this means, information might be obtained on the significance of glycogen for the sensory cells of the cochlea

I Arsacetin, the sodium salt of acetylaminophenylarsenic acid is specifically ototoxic By administering a suitable dose both the cochlea and vestibular apparatus can become completely defective in the course of a short time (Ehrlich 1907, Causse 1949, Johansen 1953) In addition to deafness and loss of vestibular function, the compound causes general poisoning resulting in the death of the experimental animal in the course of a few days (Miyamoto 1931)

A total of 16 healthy guinea pigs were used for the arsacetin experiments The animals showed a normal Preyer s reflex and normal vestibular reactions At intervals of from one to ten days after hearing had been lost, a total of 10 guinea pigs with a mean weight of 630 g were perfused with 95 % alcohol while under urethane anaesthesia The dose of arsacetin was 200 mg/kg, if a single dose did not achieve total deafness in the course of 24 hours the dose was repeated two or three times

Six guinea pigs with a mean weight of 300 g were killed by decapitation under anaesthesia and the cochlea fixed in ice cold 95 % alcohol two minutes after death, the stapes being removed and the apical winding opened These animals had been arsacetin treated with the same dose as the first ten, in which fixation had been intravital The further treatment of the fixed labyrinths was as follows all right sided cochlea were decalcified in Jenkin s solution and embedded in paraffin, while all left sided cochleae were used to make surface preparations with isolation of the stria, the organ of Corti, the spiral ganglion and the vestibular organs, using the method described by Falbe Hansen & Thomsen (1963) Surface or teased out preparations were either embedded in paraffin or stained as whole preparations (especially surface preparations of the isolated organ of Corti) In addition to staining with haematoxylin eosin and gallocyanin by Einarson's method, PAS staining was carried out The gallocyanin stained preparations will be described in a subsequent study

The haematoxylin eosin stained preparations showed a very considerable diffuse oedema of the inner and outer sulcus cells and supporting cells, especially the cells of Hensen The picture was as described by Johansen (1953) The stria showed vacuolization degeneration of the outer cell layer and migration of the pigment granules into the endolymph The membrane of Reissner had fallen

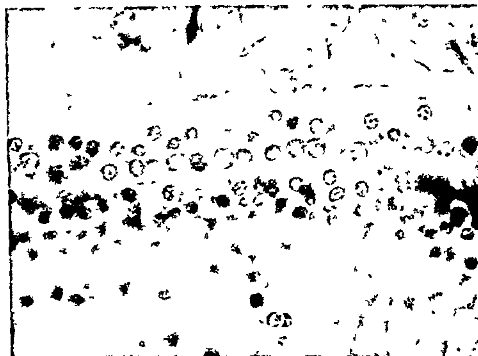


Fig 5 Guinea pig arsacetin poisoning surface preparation of organ of Corti from apical turn nucleous of outer hair cells Gallocyanin chromallun stain

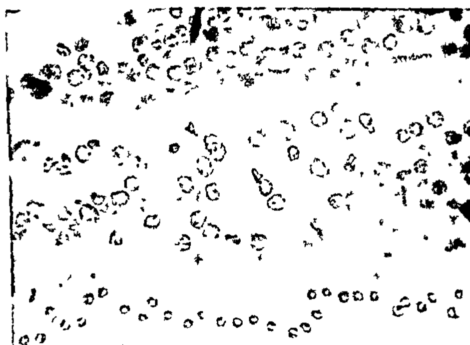


Fig 6 Guinea pig arsacetin poisoning surface preparation of organ of Corti from basal turn nucleous of outer hair cells Gallocyanin chromallun stain



Fig 7 Guinea pig arsacetin poisoning spiral ganglion PAS staining



Fig 8 Normal Guinea pig spiral ganglion PAS-staining

down on to the organ of Corti in almost all cases (following a primary distention of the membrane?) The outer hair cells showed various signs of degeneration vacuolated nuclei pyknosis intracellular oedema and even a commencing or fully developed degeneration of the cell

Examination of PAS stained preparations showed that the glycogen content

of the outer hair cells of the apical turn of the cochlea was considerably less than normal In those hair cells which were degenerating, scanty glycogen granules were found, in a position corresponding to that of the hair cells The inner hair cells, which are usually free or nearly free from glycogen, showed remarkably enough a very considerable increase in the amount of glycogen This was also the case with the cells of the spiral ganglion, which very clearly showed increased glycogen Further, while the glycogen in the normal experimental animal occurs mainly in the axon hillock, in this case it was distributed diffusely throughout the whole cell

There was no observable difference in the amount of glycogen in the preparations fixed intravitally and post mortem

II Neomycin Clinical observations on patients who have received treatment with neomycin, together with studies of experimental animals, have shown that neomycin has a toxic effect on both cochlea and vestibular apparatus (Hawkins et al 1953, Rossi & Oliviert 1959, Greenwood 1959, Halpern & Heller 1961, Lindsay et al 1960, Leach 1962) In contrast to arsacetin, which has an exceedingly rapid effect, neomycin has a slow action, and total deafness is not obtained in the experimental animal until after prolonged and heavy dosage The effect of neomycin in experimental animals is apparently reversible over an extended period, hearing seems to disappear and return, and it is often difficult to determine with certainty when total deafness has developed.

The experimental material consisted of nine healthy guinea pigs with a normal Preyer's reflex and normal vestibular reactions The weight of the animals varied from 310 to 910 g, mean value 475 g Treatment consisted of a daily subcutaneous injection of about 100 mg/kg neomycin for a period of from 24 to 48 days, until deafness developed The mean neomycin dose before total or sub total deafness developed was about 4,000 mg/kg

Intravital fixation with 95 % alcohol was carried out under nembutal anaesthesia, three days (one animal), 10 days (two animals), 30 days (5 animals) and 90 days (one animal) after the onset of deafness Subsequent treatment of the labyrinths was as in the animals receiving treatment with arsacetin

The histological findings showed some resemblance to these in arsacetin poisoning There was a considerable oedema of both inner and outer sulcus cells, especially of the latter The changes in the stria were less pronounced than in the arsacetin treated animals, and the degree of the lesions in the hair cells and spiral ganglion cells depended on the interval between onset of deafness and fixation of the tissue As late as 10 days after the onset of deafness, the organ of Corti could still be identified in the three upper turns of the cochlea, while in all the experimental animals, the organ was practically destroyed in the basal turn After a period of 30 days the organ of Corti had disappeared not only in the basal turn but also in the 2nd and 3rd turns, and in the apical turn there were only a few scattered hair cells or the remains of these By the end of three months, the organ of Corti had disappeared in all the turns

So long as it was possible to identify the outer hair cells, glycogen granules

could also be demonstrated, but only in the upper two or three turns, and in an amount which was far less than that found in normal guinea pigs

Severe degenerative changes appeared in the ganglion cells of the spiral ganglion Three days after the onset of deafness, there were numerous swollen or pyknotic nuclei, ten days after there was in addition commencing total destruction of ganglion cells, and 30 and 90 days after, the number of ganglion cells was reduced to about 1/4, the remaining cells showing pyknotic nuclei or nuclei which were in commencing degeneration In Bodian stained preparations the numbers of nerve fibres to the organ of Corti were seen to be strongly reduced, fibres could no longer be traced to the outer hair cells, while on the other hand the impression was gained that the fibres to the inner hair cells were well preserved

Corresponding to the turns where the hair cells could be identified there were a few ganglion cells containing PAS positive, diastase-digestible substance, but in smaller amounts and in another pattern than in normal cells, being diffusely distributed throughout the cell

A pronounced feature of both arsacetin and neomycin poisoned animals was that the hair cells were always affected before the cells of the spiral ganglion Changes in the spiral ganglion cells were never observed without hair cells changes

III Alloxan diabetic rats It has been demonstrated that experimental diabetes can be produced in a series of experimental animals — rabbit, dog, monkey, mouse, frog — by injecting alloxan into the circulation of the animals (Lazarow 1947) Strangely enough, the guinea pig cannot be made diabetic by the injection of alloxan, possibly because in distinction to other animals, zinc is not found in the islets of Langerhans (Okamoto 1951), or because the metabolism of the guinea pig differs in many ways from that of other experimental animals (Maske & Weings 1957)

Alloxan treated white rats were used in the present experiments A total of 15 rats with a mean weight of 155 g were made diabetic by intravenous injection of alloxan. Before the lapse of five days, however, eight rats had died from their diabetes, so that the experimental series comprised only 7 rats Four of these had normal acoustic and vestibular reflexes, two had a slightly weakened Preyer's reflex (without showing any signs of otitis media), and in the last rat, Preyer's reflex was abolished (This animal was found to be suffering from a presumably congenital aplasia of the organ of Corti) The last three animals, like the first three, had normal vestibular reflexes

Blood sugar was determined three days after the rats had been made diabetic, and on the 6th day, after having fasted for 12 to 14 hours, the animals were killed by decapitation under ether narcosis The temporal bones were fixed in ice cold 95 % alcohol not more than two minutes after the apex of the cochlea had been opened and the stapes removed The further stages in the preparation were as described for normal rats

The blood sugar varied from 212 mg% to 637 mg%, the mean value being 416 mg%

In six of the experimental animals, the cochlea was found to be quite normal PAS-staining showed the same numbers and pattern of glycogen granules as in normal animals In the animal in which Preyer's reflex had been abolished, there was as mentioned total aplasia of all turns of the organ of Corti, while the ganglion cells of the spiral ganglion were apparently normal Histological studies of the two animals with weakened Preyer's reflex provided no explanation for their reduced sense of hearing There was no sign of otitis media suppurativa, which according to Kelemen (1963) is supposed to be very common in the white rat

It may be added that PAS staining was carried out on liver biopsies from both normal and diabetic rats It was not possible to demonstrate either quantitative or qualitative differences in the incidence of glycogen in the diabetic and non-diabetic animals

DISCUSSION

Glycogen occurs particularly in tissues with a high metabolism, e g liver, muscle, kidney and nerve

In the cochlea of guinea pigs and white rats, such large amounts of glycogen have been demonstrated in the outer hair cells that it seems reasonable to draw a comparison with the depot glycogen of the liver It must be assumed that the glycogen plays a part in the cochlear metabolism, which is known to be high As already mentioned (Thomsen 1963), it has not been possible, however, to demonstrate any disappearance of glycogen as a result of prolonged acoustic stimulus

In white rats, in addition to the depot in the outer hair cells, there is a considerable depot of glycogen in the cells of Hensen It has so far not been possible to provide any explanation for the occurrence of this "depot", and for its mode of operation

In animals subjected to treatment with ototoxic pharmaca, two things seem to happen to the glycogen in the cochlea In the outer hair cells, which appear to be affected by the poison earlier and more vigorously than the inner hair cells, there is a very pronounced decrease in the amount of glycogen On the other hand, the remaining grains of glycogen seem to retain their position in the cells as the latter continue their degeneration, so that even when there is partial disappearance of the cell membrane, the cell can be identified by means of the glycogen granules In the inner hair cells and in the ganglion cells, there is a clear increase in glycogen content It is possible to imagine that under normal circumstances, these cells burn up their glycogen so rapidly that no pronounced depot can be demonstrated histologically Following the cell poisoning, the cellular metabolism is probably paralyzed, so that the glycogen supplied cannot be broken down, and can therefore be demonstrated histologically

It is probable that both arsacetin and neomycin attack the organ of hearing peripherally, the first lesions developing possibly in the vascular stria, after

which the outer hair cells are attacked and, finally, the cells of the spiral ganglion

It is not surprising that the alloxan diabetic rats did not show a pattern of glycogen in the cochlea different from that in normal rats, as the liver in the alloxan-diabetic rats also had a normal content of glycogen It is possible that if diabetic animals were exposed to acoustic stress, a reduction in the glycogen of the cochlea could be obtained which could be demonstrated histologically

Bornig et al (1958) have shown that the glycogen concentration is reduced in the liver of experimental animals which, in addition to alloxan poisoning, have received cortison treatment Studies are being instituted on such animals, to examine the glycogen content of the cochlea and the effect of acoustic stress on this

ACKNOWLEDGEMENTS

We wish to thank Mr F Tarding, Pharmacologist, and Mrs A Nielsen, Laboratory Assistant, both of Novo Therapeutic Laboratories, Ltd, for their kindness in making available their experience with alloxan diabetic rats

SUMMARY

In the guinea pig, the cochlea shows a quite definite "pattern" of glycogen distribution Glycogen is found in particular associated with the outer hair cells of the last 2—3 turns of the cochlea, decreasing in amount from the apical to the basal turn, the latter being usually quite free from glycogen The ganglion cells of the spiral ganglion contain moderate amounts of glycogen, almost always concentrated around the axon hillock The ganglion cells corresponding to the basal turn are practically always free from glycogen

The pattern of glycogen occurrence in the cochlea of the white rat is quite similar to that in the guinea pig, but in addition, the rat shows a very considerable deposit of glycogen in the cells of Hensen On the other hand, the ganglion cells of the spiral ganglion are practically free from glycogen

Alloxan diabetic rats show a glycogen pattern which does not deviate from that of the control animals

Following poisoning with ototoxic pharmaca, a series of pronounced changes occur in the glycogen pattern of the sensory cells and ganglion cells In the outer hair cells, these changes are seen as a very pronounced decrease in the amount of glycogen, while in the inner hair cells the amount of glycogen increases The latter effect is also seen in the ganglion cells of the spiral ganglion

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THE SELLA TURCICA AFTER TRANSSPHENOIDAL HYPOPHYSECTOMY — A RADIOLOGICAL AND X RAY MICROSCOPICAL STUDY

By

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Hypophysectomy is performed in man under three main conditions 1) in order to remove pituitary tumours 2) to arrest a rapid progression of a malignant metastasing tumour or 3) to reduce the retinopathia in severe diabetes mellitus There are two main surgical approaches to the pituitary gland the cranial and the transsphenoidal way Several different transsphenoidal interventions of the pituitary have been reported The most common during recent years is the external transethmoidosphenoidal (Escher 1962) and the transantro-sphenoidal method (Hamberger et al 1961)

About six to twelve months after a transantro-sphenoidal hypophysectomy a radiopaque structure is seen in the posterior part of the sphenoidal sinus on the macroscopical radiograms (Rådberg 1963) By tomograms it was found that this newly formed structure had a different density in different regions (Fig 1) A og B Corresponding to the operation defect and in the adjacent part of the sphenoidal sinus the density is somewhat lower than in surrounding bone but higher than in the soft tissues Corresponding to the praesellar area and to the walls of the posterior part of the sphenoidal sinuses the density is about the same or some-

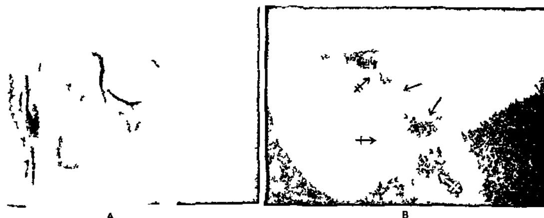


Fig 1 Tomogram of the sella turcica region before and after transantro sphenoidal hypophysectomy 53 year old woman with breast cancer A) lateral tomogram through midline of normal sella preoperatively B) lateral tomogram of the sella 20 months after transantro-sphenoidal hypophysectomy In the operative defect (→) there is a soft tissue continuing into adjacent parts of the sphenoidal sinus (→) In the posterior part of the sphenoidal sinus and in the presellar area the bone is thickened and sclerotic (//→)

what higher than in normal bone From the roentgenograms alone is was difficult to determine the nature of these structures with certainty (Fig 2) Three possibilities might be considered, namely a dense organic tissue, osteoid tissue, or bone In order to solve this problem the sphenoidal bones from four lethal hypo-

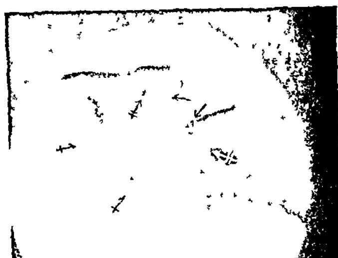


Fig 2 Lateral tomogram through a specimen of the sellar region from an operated case Operation defect (→) soft tissue (→) sclerotic thickening of bone (//→)

physectomized cases of metastasing tumour have been studied with aid of X-ray microscopy Plane parallel ground sections from the sagittal plane of the region mentioned above have been put in close contact with a very fine grained film emulsion (Kodak Spectroscopic Plate No 649) (Hallen and Rockert, 1960) Calcium has an absorption edge at 3 07 Å As organic tissues have a negligible X ray absorption within this wave length region the microradiograms show the mineral distribution within the section Thus white areas on the emulsion correspond to parts rich in calcium The lateral resolution is due to five different factors the size of the grains in the film emulsion the distance between specimen and emulsion the size of the focal spot, the distance between focus and specimen

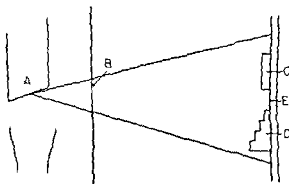


Fig 3 General arrangement for microradiography A = the target of the X ray tube B = the window filter C — the sample D — reference system E = the photographic emulsion

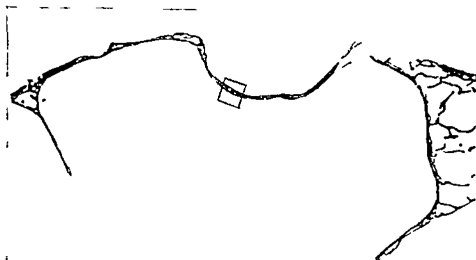


Fig 4 Microradiogram of a normal sella turcica. Orig magnification × 2

and the thickness of the specimen Under optimal conditions a lateral resolution of about 0 8 μ can be obtained In the present investigation a Machlett X ray tube (OEG — 50) has been used (Focus — specimen distance 300 mm Specimen thickness 75–100 μ) Using a reference system with known azsorption coefficients densiometric measurements can be made thus giving quantitative information of the mineral distribution (Fig 3)

The specimens obtained from the four cases have been compared to twenty normal anterior walls of the sella turcica from an autopsy material The relationship of the sphenoidal sinuses to the sella turcica is inconstant, the former varying greatly in size and shape From a practical clinical standpoint it is appropriate to divide sphenoidal sinuses in three types a conchal, a praesellar and a sellar type The sellar type is the largest and offers the best anatomical conditions for transsphenoidal hypophysectomy The thickness of the anterior wall of the sella is 0 5 ± 0 21 mm in cases with sellar type of sphenoidal sinuses (Hammer and Rådberg 1961) All cases in the present investigation had sphenoidal sinuses of the sellar type The thin normal anterior wall of compact bone is shown on microradiograms in Figs 4 and 5 Using small magnification this was also shown on microradiograms by Mahmoud el Sayed (1958) In larger magnification it is possible to distinguish separate Haversian systems Osteons of varying ages can be seen Young osteons are less mineralized and appear dark on the picture The concentric lamellae within an osteon are visible The interstitial lamellae areas are the most complete mineralized parts being remnants of old osteons External and internal ground lamellae also appear in the thin osseous sellar wall (Figs 4 and 5)

In the operated cases, however the praesellar area and the remaining parts of the frontal wall of the sella and the posterior parts of the wall of the sphenoidal sinus developed into a very thick compact bone structure (Figs 6 and 7) The thickness of this structure increased about 5 times About twelve

months after surgery several Haversian systems of varying ages are seen However, their number per unit area is less than those of the control material This suggests a lowered local metabolic activity Incomplete ground lamellae are observed in the newly formed bone structure in the operated cases Corresponding



Fig 5 Microdiagram of a normal sella turcica Orig magnification × 8 From marked area of Fig 4



Fig 6 Microradiogram of the region around the sella turcica of the same case as in Fig 2 Orig magnification 2



Fig 7 Microradiogram of the region around the sella turcica of the same case as in Fig 2
Orig magnification × 8 From marked area of Fig 6

to the operation defect in the anterior wall and the floor of the sella turcica there is a dense organic membrane which separates the sella turcica from the sphenoidal sinus This can be seen in ordinary light microscopy

Thus the newly formed radiopaque structure seen postoperatively in the posterior part of the sphenoidal sinus consists of two different tissues In the area of the operation defect and in the adjacent part of the sphenoidal sinus it consists of dense organic tissue and the remaining surrounding walls show newly formed compact bone

As shown by Harris in 1960 tetracyclines are deposited in bony tissues under going mineralization at the moment of administration A single dosage of 1 gm is enough in man to produce a yellowish green fluorescence in ultra violet light. This appears as brilliant rings in the Haversian systems Most of the tetra cyclines are absorbed on the surface of the hydroxy apatite crystals and may in this way become built into the bone The fluorescence may stay as long as the area is not demineralized Periods of intact fluorescence up to nine years have been reported

Two of our hypophysectomized cases have been treated with tetracycline for a week, six months after the operation Fluorescence microscopy of ground sec tions of the sellar region one year after surgery, shows the tetracycline mainly localised just below the surfaces of the mineralized walls of the sella Apparently only a small part is mineralized after the antibiotic administration This suggests that the reparative activity in the tissue has its greatest extent immediately after the operation and afterwards gradually decreases This is supported by the microradiographic findings which show a very stable mineralization pattern one year after surgery

SUMMARY

About six to twelve months after transsphenoidal hypophysectomy a radiopaque structure is seen in the posterior part of the sphenoidal sinus Light, X-ray, and fluorescence microscopy after tetracycline administration have shown this structure to consist of two different tissues, a dense organic matrix and newly formed compact bone Postoperatively the remineralization activity in the rebuilt area decreases gradually being very minute after a year

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CHANGES OF AGING IN THE INNER EAR AND THE INNER EAR DIABETES MELLITUS HISTOLOGICAL STUDIES

By

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Even to this day there are *conflicting views regarding the pathology of a* conditioned hearing loss This is presumably due first and foremost, to difficulties connected with histological studies of the inner ear, especially human material, i e, postmortem autolysis fixation decalcination, dehydrati *and embedding All the steps of this procedure may give rise to artifacts a* consequent misinterpretations In his investigations into age-conditioned stru*tural* changes of the inner ear Fleischer (1956) classified the changes definit as age-conditioned only if they were found to progress with age

At an early stage it was realized that the hearing *loss* in elderly people mig have a number of different causes Thus Mayer (1920) made a distinction betwe (1) the age conditioned hearing loss which invariably occurs with advancing ag (2) the hearing loss due to diseases of aging mainly arteriosclerosis, and (3) hea ing *loss* independent of age In analogy to the *loss* of elasticity in the lens of t eye, he assumed that the aging process in the inner ear was due to increas rigidity of the basilar membrane spreading from the base to the apex of t cochlea In this membrane he claimed to have demonstrated hyalinizatic thickening, and even depositions of calcium

Saxen and von Fieandt (1937) made a thorough study of the temporal bon of 33 patients who had attained a ripe old age Two kinds of changes we found First, the senile atrophy of the spiral ganglion, which had also been d scribed by previous authors Secondly in more than half the cases, severe chang of the cochlear duct, viz, flattening of the strial epithelium, hyalinization of tl blood vessels in the stria vascularis depositions of pigment, collaps of Corti organ, and adhesion of Reissner s membrane to the strial epithelium The changes were equally marked in all parts of the cochlea and were assume to be caused by the capillary sclerosis in the stria vascularis Consequently, tl condition was named angiosclerotic inner ear degeneration

Studying inner ear changes in old cats and in a 70 year old man, Schuknecl (1955) found changes very similar to those described by Saxen and von Fieand viz, ' epithelial atrophy ' characterized by flattening of the epithelium in th basal part of the cochlear duct, decreasing toward the apex, and ' neutral atro phy" consisting in loss of ganglion cells in the basal part of the spiral cana starting a small distance from the *basal end of this canal*

In 100 temporal bones representing all age groups, Fleischer (1956) detecte as the only change with age-conditioned progression, a loss of ganglion cells i

Table I

Case	Pneuma tization	Sclerotic bone around the labyrinth	Decal cified areas	Flattened *cochlea*	Family history of o i
1	+++	+	+	?	—
2	+	+	—	—	+
3	+++	+	—	+	+
4	+++	+	—	+	+
5	+++	+	+	+	+
6	+++	+	+	?	—
7	+++	+	—	+	—

three cases without hereditary influence Tomography of the labyrinth was carried out on seven of these patients with fully developed osteogenesis imperfecta The results were then *compared with those obtained from audiometry and* observations made at operation Table I gives a survey of the roentgenological findings The tomographical examinations of the labyrinths have been carried out with Polytom[1]

Roentgenographic examination showed, in all cases except one, an extensive pneumatization with large cell systems right out in the pyramid apices The *exception was a patient who had undergone radical operation on both sides*

In contrast to the extensive pneumatization there was sclerotic bone or irregular structure around the labyrinth The sclerotic bone even surrounded the porus acusticus internus, which in 3 cases was compressed in the medial portion, a deformation which could be due to bone fragility

In three cases there were circumscribed decalcified areas in the walls of the cochlea In case (V C 300913) these changes were so extensive that only fragments of the cochlear walls were visible (Fig 1) Changes of this type have not previously been shown roentgenographically

In four cases, of whom 3 did not have the decalcified areas described above, we could show a flattening of the basal turn of the cochlea A flattening of the cochlea has previously been described by Fowler in his work on osteogenesis imperfecta

From the audiological point of view case 1 is of especial interest (Table II and Fig 2) Although the audiogram showed a severely reduced bone conduction, discrimination was normal This we interpreted as a sign of a conductive defect in the inner ear, and exploration of the middle ear supported this inference At operation the stapes was found to be movable, but the light reflex from the round window did not change when pressure was put upon stapes The defect did not lie in the round window itself, as shown by the fact that perforation of the window membrane produced leakage of perilymph It thus appears that a transmission defect exists in the inner ear in this case

[1] A more detailed description of the tomographical technique in the examinations and the roentgenographic findings will be published in Acta Radiologica

It is interesting to note that there seems to be a connection between the roentgenographic findings and the family history

Ruttin 1936, reported that in patients with osteogenesis imperfecta combined with hearing loss of otosclerotic type the disease was hereditary, whereas in those



Fig 1 Tomography of the labyrinth in abnormal ear (upper) and in a case with osteogenesis imperfecta (lower) 1 cochlea, 2 incus

Table II *Clinical symptoms in 7 cases of osteogenesis imperfecta*

	Fractures	Blue sclera	Hearing Loss: Tone audiogram: Air db Rt	Air db Lt	Bone db Rt	Bone db Lt	Speech audiogram: Hearing level for speech db Rt	Hearing level for speech db Lt	Discrimination per cent Rt	Discrimination per cent Lt	Remarks
13	>5	+	70	88	45	50	73	74	92	94	Lt ear exploration 1962 mobile stapes See text.
08	10	+	32	67	3	17	35	65	96	92	Rt ear fenestration op 1956, stapes fixated.
120	46	+	43	47	13	10	38	47	94	100	Lt ear stapedectomy 1963, the ossicle chain normal, stapes fixated
17	11	+	deaf	3	deaf	3	deaf	3	deaf	96	
24	4	+	57	80	25	32	47	73	92	74	Rt ear fenestration 1959 Fistula closed
01	5	+	deaf	deaf	deaf	deaf	deaf	deaf	deaf	deaf	
20	9	+	43	35	12	5	40	42	98	88	

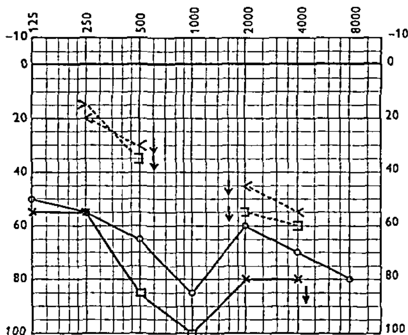


Fig 2 Tone audiogram in osteogenesis imperfecta (300913 V C)

with inner ear lesions it was not Cases 1, 6 and 7 in our material lack this family history and showed defects in the walls of the cochlea which probably are the cause of the hearing loss

As the histological changes within the labyrinth in osteogenesis imperfecta are similar to those of otosclerosis, it is reasonable to investigate whether in so called cochlear otosclerosis changes in the cochlea can be shown by roentgenographic examination 21 cases of clinical otosclerosis with pronounced sensory-neural loss, judged by tone and speech audiometry, have been tomographed In three cases, pathological changes have been found that are of essentially the same type as in osteogenesis imperfecta

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DISCUSSION

Opheim to Lidén

In otological literature there are probably not more than two histologically examined cases van der Hoeve de Kleyn's syndrome in which otosclerosis was found They are those found by Ruttin and Gimplinger It is to be noted that the cause of loss of hearing in the van der Hoeve de Kleyn's syndrome is more often neurogenic than is the case in otosclerosis

In addition to this a great many reports have been published on unsuccessful results of fenestration operations in these cases As far as I have understood Liden he has in one case, apparently, found no stapes fixation — and has on account of this presumed that a trans mission hindrance was present in the inner ear I believe that in this syndrome a stape fixation is not the cause of the matter

I have seen the following in two cases A fibrotic stapes crura which was unable to convey sound energy from the incus to the stapes plate, in other words a lack of continuity in the ossicular chain

REFLEXIONS ON THE RESPIRATION IN NEUROSURGICAL PATIENTS IN COMA WITH REFERENCE TO BLOOD GAS ANALYSIS AND BRAIN STEM LESIONS

By

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On a neurosurgical ward one meets patients in sopor and coma It is important to ensure open air passage in such circumstances So the ENT-surgeon naturally takes his place in a team treating patients in coma The tracheotomy is performed by the ENT surgeon, who afterwards controls the airways together with the anesthethists Using catheter suction, sometimes also the bronchoscope, they maintain a free air passage Stagnation of secretion deep in the bronchial tree is a hazard leading to atelectasis and further to diminished alveolar ventilation This is a step towards reduction in blood oxygen and accumulation of carbon dioxide An increase in blood CO_2 itself will in turn give rise to more secretion in the bronchial tree

While maintaining a free air passige during coma, the feeding through a gastric tube must be provided for, considering the need for an adequate amount of calories, minerals and electrolytes

In every stage of the coma respiration must be at a sufficient level One question can be asked It is possible that behind the comatous appearance a situation of hypoxia or hypercapnia exists? To some extent hypercapnia can be traced by measuring the alkali reserve in venous blood A complete evaluation of the respiration however is possible only by arterial blood gas analysis This procedure indicates the oxygenation of hemoglobine (HbO_2), the total amount of carbon hydroxide concentration (TCO_2), and actual tension of carbon dioxide (pCO_2) It also includes assessment of pH in blood In addition to blood gas analysis actual values of electrolytes, hemoglobine, nonprotein-N and hematocrite are of importance

Faced with a patient in any stage of coma the clinical evaluation of respiration may give an impression of normal breathing, hypo- or hyperventilation The correctness of a meer clinical view afterwards may be verified or adjusted A pathological process in the lungs may give rise to temporary disturbances in the alveolar gas exchange If such a process be eliminated the pathological type of respiration may give way to normal conditions

The correspondance between pH in blood and the carbon hydroxide components is expressed by the equation

$$pH = pK + \log \frac{(HCO_3^-)}{a \ pCO_2}$$

$$\text{where } (HCO_3^-) = \text{Tot } CO_2 - a \ pCO_2$$

Changes in the carbon hydroxide concentration and carbon dioxide tension will highly influence the pH of blood When the latter leaves its normal value in arterial blood (7 42), as a consequence of either hyper- or hypoventilation, the effect will be respiratory alkalosis or acidosis In other situations pH remains normal while the carbon dioxide components establish a balance between mutual abnormal values This *means a compensation of respiratory alkalosis or acidosis*

An interpretation of blood gas analysis incorporates also an evaluation of a present metabolic influence upon pH and the carbon hydroxide concentration in blood The role of renal function is decisive for both metabolism and balancing the blood electrolytes A renal metabolic factor can only to a certain extent be compensated by the alveolar ventilation The close relationship between metabolism and alveolar function therefor calls for blood gas analysis and electrolyte measurements parallel in time This is still more important in comatous patients who are subjected to artificial feeding

The complex function of respiration is a result of alveolar ventilation governed by the central nervous regulation in the mesencephalon, pons and medulla oblongata Within these parts are located respiratory centers for rhythmicity, inspiration and expiration, upon which act three stimuli of principal nature, viz the CO_2 concentration in the blood, pH of blood through aortic and carotic glomus bodies, and the vagal reflexes attributable to the degree of distension in the lungs

The blood flow to the brain is very rich and provides ample supply of oxygen and disposes of carbon dioxide The rich arterial supply to the basal parts of the brain is yielded by the vertebral arteries, the basilar artery and branches supplying the brain stem with its vital centers for respiration and the reticular formation

Within the skull the flow of blood is influenced by an increase of the intra cranial pressure, the origin of which may be traced above or below the tentorium Both increase in pressure or expanding pathological processes tend to cause coning or brain herniation So the brain stem may be displaced or compressed. Such abnormal conditions will have influence upon arterial or venous flow Stasis, infarction or necrosis of the brain will develop

11 patients were followed for a long period, while their respiration, electrolytes and consciousness were subjects of observation

3 patients were placed in one group based on a hypothetic initial brain hypoxia (cerebral hemorrhage, strangulation, trombosis of one vertebral artery and hypogenesis of the opposite) In coma they breathed spontaneously and the blood oxygenation measured 90 % As a common feature the respiratory frequency was increased, and pH indicated respiratory alkalosis In one case carbon hydroxide concentration and carbon dioxide tension were subnormal, from which might be suspected a decrease in CO_2 stimulation of the respiratory centers Necropsy findings in this case demonstrated a large infarction within the brain stem, *due to an extreme reduction of blood through the basilar artery* The electrolytes were normal in all cases of the group

A second group consisted of 4 patients, all victims of skull fracture Their respiration while in coma was spontaneous and the blood oxygenation amounted

90 % Other readings from blood gas analysis and electrolytes proved normal Clinically too their type of respiration was normal 1 patient died in coma after 42 days Necropsy showed tracheobronchitis, cerebral coning and several cavities scattered in the mesencephalon and pons 1 patient cleared up from his coma but remained mentally confused After a course of 4 months from the date of his skull fracture the patient died The necropsy findings were massive bronchopneumonia and a large infarction of the central parts in the mesencephalon (1 3 × 0 5 cm)

4 patients formed group number three They were operated on for brain tumours of different natures (meningeoma, meningeoma plus arterio venous aneurysm and bulbar paresis, tumour of the cerebellopontine angle) They showed no common characteristics as to types of respiration, electrolytes or blood gases 1 patient with meningeoma (from the sphenoideal bone) developed hyperventilation and alkalosis He died 2 weeks after craniotomy with bronchopneumonia and a large pontine infarction A second patient died in coma after 3 months, maintaining spontaneous respiration until death throes The postmortem investigation diclosed a gliomblastoma infiltrating one half of the transveral section through the mesencephalon One might on this background suppose the respiration to be directed from intact respiratory centers opposite the midline One patient lived for more than 2 years, mentally adequate, after resection of a cerebellopontine angle tumour Necropsy findings demonstrated a large infarction filling the ipsilateral half of a section through the pons Still the respiration remained sufficient 1 patient underwent tracheotomy for bulbar paresis, to avoid the risk of aspiration He succumbed to a massive bronchopneumonia, before a retracheotomy could be performed to ensure relief from mucous in the bronchial tree Postmortem brain examination showed a pontine infarction, but apparently without close relationship to the respiratory centers

8 patients of 11 died and were made subjects to postmortem brain studies Some examples from the microscopical preparations indicate as conclusive remarks

1 A large pontine infarction following vertebral artery trombosis, caused disturbance to the central respiratory regulation A short coma with abnormal blood gas values ended fatally In this case the lungs did not demonstrate changes which alone could be responsible for the fatal course
2 In spite of infarction of the brain stem some patients breathe spontaneously Some too remain conscious At necropsy, however, pathological findings in the lungs seemed to be the cause of death
3 The growth of a mesencephalic tumour of an infarction destroying one half of the cross section through the brain stem, still permits spontanous respiration It is to be supposed that corresponding tissues on the opposite intact side keep up the capacity triggering the respiration

SUMMARY

The after care of comatous patients suffering from brain lesions and skull fractures calls for tracheotomy Even patients in a conscious state while victims to bulbar paresis need the advantage of the same precaution The clinical evaluation of respiration during coma usually gives the correct answer as to its efficiency However, blood gas analysis and measurements of the blood electrolytes on the other hand give the complete picture of pH, oxygenation and CO components during a course of observation Such records are of particular importance in an attempt to exclude that the coma originated from hypoxia or abnormal carbon hydroxide values Postmortem findings retrospectively indicate that lesions in mesencephalon and pons may develop to a small or large extent The respiration may still remain spontaneous during long lasting coma, with normal readings of the blood gases

RESPIRATORY VIRUSES IN MODEL EXPERIMENTS

By

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Respiratory Viruses in Model Experiments

In tissue cultures viruses can multiply and destroy dedifferentiated cells even from organs otherwise not affected by the virus in question

In histologically and functionally intact organ culture it should presumably be possible to study the specificity of infection If viruses were found to multiply in organ cultures and to produce histopathological changes resembling those in the infected intact host, this technique should enable us to study the stages of infection under standardized conditions in model experiments

Laboratory animals rarely lend themselves to experimental studies of viruses capable of infecting the human respiratory tract

Despite the ubiquity of human respiratory viral infections, comparative viro logical and histopathological studies are meagre or lacking even of influenza, as pointed out by Mulder 1960 (1) for example

It was thought that it might be possible to infect organ cultures of ciliated epithelium with respiratory viruses in model experiments

In contrast to experimental animals or human volunteers, cultures enable examination of quantitative assessment under bacteria free conditions

In addition, material from part of the organ in question can serve as control for infected parts of the same organ The explants may also be used for histo logical examination at suitable intervals

HISTORICAL

Carleton 1925 (2) was the first to observe ciliary activity of a few days' duration in tissue culture

Later researches have been able to preserve ciliary activity for several weeks

Barski et al 1957 (3) and 1954 (4) studied explants of foetal and adult human and adult monkey ciliated epithelium for their resistance to several viruses The resistance to polio, adeno and rhino tracheitis viruses was high, that to herpes and vaccinia viruses less high

Bang and Niven 1958 (5) maintained embryonic human tracheal fragments for periods up to two months and found them insusceptible to chick adapted influenza virus Adult ferret nasal epithelium was susceptible to the W S strain of influenza virus, which destroyed the surface cells Similar tissue taken from ferrets immune to the influenza virus was equally susceptible in vitro

Bang 1959 (6) infected organ cultures of human embryonic trachea with an influenza A_0 strain Infection was established but it produced no gross pathologic changes

Bang 1961 (7) who infected organ cultures of chick respiratory tract epithelium with the myxovirus N D V found the number of infected cells to be astonishingly low

Maddi 1963 (8) used adult human bronchial epithelium for organ culture studies Infection with adenovirus 3 was followed by the appearance of inclusion bodies in some of the epithelial and ciliated cells

All these earlier investigators used serum in the medium, and recorded secondary growth of dedifferentiated cells

MATERIALS AND METHODS

Tracheas from rabbits and human foetuses were cut into pieces of at most 5—6 square millimeters The cartilage was retained as scaffolding for the ciliated epithelium

Attempts were made to find the most favourable composition of the medium Optimal temperature and pH were determined It was found possible to culture these explants in a medium devoid of plasma and serum namely in Parker medium 199, and to maintain them almost as long as when serum had been added to the medium This procedure prevented secondary outgrowth of dedifferentiated cells in which viruses can multiply and interfere with titration studies

Ciliary activity was taken as a readily observed measure of the function of ciliated epithelium The explants were kept in translucent plastic Petri dishes and examined daily for ciliary activity under a microscope with the aid of reflexes from incident light The test was based on the all or none law i e presence or absence of ciliary activity The histological examinations indicated that disappearance of ciliary activity probably meant that the ciliated cells were also morphologically altered A suitable number of explants were taken at suitable intervals for histological examination

The viruses studied were Influenza virus type A_0 adeno virus type 2 and 7, para influenza 1 (Sendai) herpes simplex virus and polio virus type 1

Influenza virus titers were expressed as infective doses for embryonated eggs and the other viruses as infective doses for tissue cultures

The explants were kept at 37° C in high humidified environment The medium devoid of plasma and serum was added until it was flush with the ciliated surface of the explants

RESULTS

Most of the uninfected explants from rabbit tracheas maintained their ciliary activity as long as 4—6 weeks at most 8 weeks Human embryonic tracheal explants could generally be maintained for 3—5 weeks a few up to 7 weeks

Organ cultures of trachea from 45 rabbits proved insusceptible to the viruses



Fig 1 Ciliated epithelium from human embryonic tracheal explant maintained 10 days as organ culture (All specimens were fixed in Bouin s solution and stained with haematoxylin and eosin)

investigated with the exception of herpes virus, which totally destroyed the epithelium, as it did in the explants from human embryos Daily inoculation with influenza virus for periods up to two months produced no demonstrable toxic effect

Organ cultures from 140 human foetuses 8—55 cm long were used

In a few experiments they proved to be unaffected by polio virus type 1, which did not multiply in the explants either

Inoculation with influenza A_2 virus affected 80 of 96 foetuses In most of the cases virus was harvested in a much higher amount than that inoculated Virus has been successfully carried through successive cultures from 22 other foetuses with high titers As a rule, ciliary activity ceased a few days or a week after inoculation At the same time typical histopathological changes appeared The ciliated cells were shed and the cytoplasm of the intermediary cells became swollen and the cells lost their boundaries

In this amorphous-looking cytoplasmatic mass the nuclei remained less affected for a fairly long time The intermediary cell layer gradually decreased, and after a few weeks it almost disappeared During the whole time the basal cell layer and the basement membrane were apparently intact

(Fig 1 Control material after 10 days in organ culture Figs 2 and 3 explants inoculated with influenza A_2 virus 4 and 17 days previously)

The histopathological picture resembles that of material obtained from ciliated respiratory epithelium in ferret infected with influenza virus (Stuart-Harris 1953

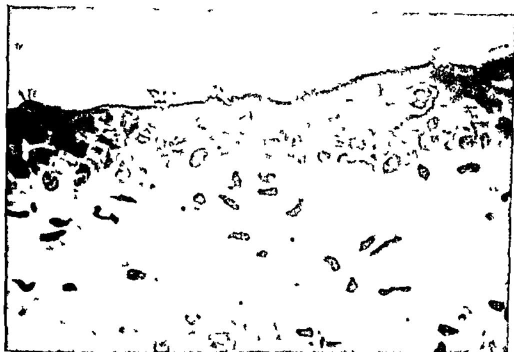


Fig 2 Explant from the same foetus as in Fig 1 after 4 days incubation with influenza A₀ The virus was inoculated on the second day after exploration Only occasional ciliated cells are left



Fig 3 Explant from the same foetus as in Fig 1 og 2 17 days after inoculation with influenza A₀ No ciliated cells are seen The intermediary cells are melted into an amorphous looking mass with interspersed degenerating nuclei The basal cell layer and the basal membrane are seemingly unaffected This explant is capable of virus production

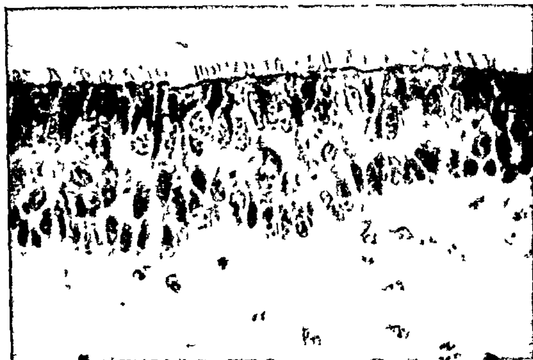


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(Fig 1 Control material after 10 days in organ culture Figs 2 and 3 explants inoculated with influenza A₂ virus 4 and 17 days previously)

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disappeared The titer in the medium was always low When the cells were destroyed by freezing or by infection with influenza virus adeno virus could be demonstrated in high titers

Herpes simplex virus destroyed the entire epithelium and the stroma cells within a few days Typical intranuclear inclusion bodies appeared (Fig 5) The virus producing cells were rapidly destroyed to such an extent that a day or so



Fig 5 Explant inoculated with herpes simplex virus 3 days previously The epithelial cells seen in the top half are enlarged by intranuclear inclusion bodies that displace the chromatin material to the periphery In the bottom half are smaller but likewise affected stroma cells

after disappearance of the ciliary activity no virus could be detected in the medium

Sendai virus seemed to multiply in these organ cultures and could be transferred in series but not so easily as influenza virus In several cases the explants inoculated with Sendai virus appeared to undergo histopathological changes, perhaps in a characteristic way, but the material hitherto studied is not large enough to allow valid conclusions

DISCUSSION

Human embryonic tracheal explants in organ culture seem to lend themselves to comparative virological and histopathological studies with quantitative assessment Other human respiratory viruses can probably also be studied in this model system Since these organ cultures, in contrast to dedifferentiated cell cultures, reacts specifically to viral infection, they may prove to be valuable as bioassays for testing antiviral drugs

SUMMARY

Organ culture of adult rabbit trachea proved resistant to inoculation with polio, influenza A_0, para influenza 1 and adeno virus, but was readily destroyed by herpes simplex virus

All of the above mentioned viruses with the exception of polio probably multipled in organ cultures of the ciliated epithelium of human embryonic explants These viruses can abolish the ciliary activity through cell destruction and produce characteristic histopathological changes

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MENINGITIS IN CHILDREN AND ITS EFFECT ON THE ACTION OF THE INNER EAR

By

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According to Wilson (1955) postnatal deafness or severe hardness of hearing in children is mostly due either to labyrinthitis or to toxic damage of the labyrinth. Labyrinthitis, again, is generally secondary to meningitis. In Schambaugh's series of 1928, meningitis was the main reason for deafness in 17.5 per cent of 1192 pupils of the school for deaf children. Best, in this report of the same year, mentions deafness in 14.5 per cent, and Yarsley (1934) in 13 per cent of their series. In studies performed during the antibiotic period, almost the same percentages have been obtained. Bordley in 1952 stated that meningitis was the cause of deafness in 9 per cent of 485 cases and parotitis in 1 per cent. In 1953, Kinney published a report in which considerably higher percentages are given: meningitis caused deafness in 23.9 per cent and parotitis in 10.6 per cent, only unilateral hearing damage occurred in all these cases, however. In Fowler's (1954) series of 189 children, the cause of deafness was meningitis in ten, and parotitis in eight. In only five of 112 children with unilateral hearing loss, Everberg (1957) established that this was definitely due to epidemic parotitis. The cause of hardness of hearing due to parotitis was, according to Lindsay (1960), virus infection resulting in endolymphatic labyrinthitis. Holmgren (1952) considers epidemic parotitis the commonest cause of unilateral deafness. On study of the above mentioned figures it should be remembered that parotitis meningitis may appear completely without subjective symptoms, even if the leukocyte count in liquor is 9000, as in Wesselhoft's investigation of 1943.

Meningitis is thus a frequent postnatal cause of deafness and severe hardness of hearing. In the present study, we have made an endeavour — on the basis of follow up examination — to clarify how childhood meningitis affects the action of the inner ear. Our series comprises 47 children, treated for meningitis at the Childrens' Clinic of the University Central Hospital, Turku, or at the Epidemic Hospital of the City of Turku, in 1953—1957. A request was sent to the parents of 223 patients to permit their children to appear for follow up examination and preliminary questioning with regard to deafness and disturbances of the vestibular organ. 105 parents were not reached owing to the wrong address available, and 12 replied that their children were quite well and not in need of follow-up examination. In addition to careful study of the patients history, an endeavour was made to exclude all other causes of deafness: prenatal, natal and other postnatal causes. Close otorhinolaryngological examination was made, including pure-tone tests, speech audiograms when necessary, and caloric tests according

to Hallpike If the caloric test gave no reaction, ice water and rotation tests were made If the vestibular organ did not react even to these tests, its action was considered completely extinguished.

Table I gives the patients' average age, 5 years and 6 months, at the time of sickening, the distribution of the patients in the groups of nursing age, pre-school age and school age, and the number of cases of inner ear disturbances in each group

In Table II the patients are divided according to the primary diagnosis, average age at the time of sickening, average period of treatment, and highest average leukocyte count in liquor during the illness in the different groups of diagnosis, and distribution of inner ear complications in the various groups of diagnosis

Table III shows the distribution of the patients according to the highest leukocyte count in liquor, and the number of patients with hearing defects in these groups is given

Table I *Age at time of illness and inner ear complications*

Age	Number of Cases	Inner ear complications
< 1 year	12	2
1– 7 years	18	4
7–15 years	17	3
Total	47	9

Average age at time of illness 5 years 6 months

Table II

Diagnosis	Number of Cases	Average age at time of illness	Average period of treatment	Average of highest cell counts	Inner ear complications
M. serosa	23	9 years 1 month	15 days	138	1
M. purulenta	13	2 years 4 months	27 »	6900	4
M. parotidea	8	7 years 7 months	12 »	390	1
M. tuberculosa	3	6 years 4 months	6.5 months	360	3

Table III *Cell count and inner ear complications*

Highest cell count in liquor	Number of cases	Inner ear complications
< 100	10	1
100– 500	20	2
500–1000	4	2
>1000	13	4

Table IV.

Patient	Diagnosis	Age at time of illness	Cell count	Period of treatment days	Loss of hearing	125	250	500	1000	2000	4000	8000	Vestibular reaction
O L	M	1 month	10 000	36 days	right	>75	>80	>100	>100	>100	>100	>80	right —
2	purulenta				left	>75	>80	>100	>100	>100	>100	>80	left —
E T	»	11 months	25 000	27 »	right	>70	>80	>100	>100	>100	>100	>80	right —
3					left	>70	>80	>100	>100	>100	>100	>80	left —
H K	»	14 »	14 900	45 »	right	25	20	20	20	0	0	0	right —
32					left	0	0	10	0	0	0	35	left —
P P	»	1 year and			right	10	0	0	0	0	0	10	right +
31		8 months	3 500	27 »	left	35	25	35	25	5	0	10	left +
T M	M	3 years and			right	45	40	45	45	30	10	60	right +
34	tuberculosa	2 months	600	7 months	left	0	0	0	0	0	50	50	left +
A H	»	4 years and			right	0	0	0	0	0	0	0	right +
9		10 months	250	6 »	left	0	0	0	0	0	0	0	left —
K V	»	11 years	246	6 »	right	15	5	0	0	5	10	80	right +
33					left	15	5	0	0	0	10	65	left +
M P.	M	9 years and			right	10	0	0	10	20	20	40	right +
	parotidea	5 months	605	10 days	left	5	0	0	10	25	35	30	left +
H H	M serosa	12 years	52	18 »	right	5	0	5	10	5	25	55	right +
37					left	50	50	55	65	55	65	55	left —

In Table IV, nine patients with disturbed function of the inner ear are presented age on sickening, period of treatment, and highest leukocyte count in liquor during the period of illness

On study of the results of the present investigation it was observed that the disturbances of the inner ear function were similar to those caused by meningitis, previously reported in the literature

As to the followed up examination — since the patients were not examined prior to sickening we can only assume, but not state definitely, that the changes were caused by meningitis, after ascertaining that no prenatal, natal or other postnatal causes occurred Both the completely deaf patients had high leukocyte counts in liquor and, in addition, the period of fever and illness was longer, compared with the other infants of nursing age In addition to hardness of hearing, the vestibular function of patient H K was completely extinguished on both sides, he was only a year and some months old at the time of sickening the leukocyte count in liquor was much higher than the average, and the period of fever and treatment was longer than the average

SUMMARY

A series of 47 children were re examined In 1953—1957 they had been treated for meningitis The whole inner ear function of two patients was completely extinguished In six, perceptive hearing loss of various degree occurred — generally worse on one side The audiograms were falling or rising toward the high frequencies, or were horizontal In one of the patients with hardness of hearing the vestibular function was completely extinguished In one the vestibular function was extinguished on one side, but hearing was quite normal on both ears It was observed that, the higher the number of leukocytes in liquor, the longer the duration of the disease, and the lower the patient's age, the greater was the injury, even causing complete deafness The most significant of these factors was, however, the duration of the disease

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MENIÈRE'S DISEASE — PATHOLOGY AND PATHOGENESIS

By

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About a hundred years ago Meniere described the symptocomplex which rightly bears his name inasmuch he pointed out that it was a labyrinthine disease and not a brain disease and at the same time described the symptomatology so well that not much new has been added since

He also made a plea for histological examination of temporal bones on such patients which however first took place in 1938, when Hallpike and Cairns described the endolymphatic dilatation On background of the enormous literature about Menière's disease pathological anatomical publications are rare It can be mentioned that Altmanns survey of the literature from 1955 contains 245 references with seven pathological anatomical studies, and that Neveu in another survey from 1962 covering the period from 1957 to 1962 has 200 literature references of which only 6 are about pathological anatomy Our knowledge about the pathology in Meniere's disease is therefore limited and about the pathogenesis we only have guesses

It is important, that Meniere's disease only is diagnosed when there is fluctuating hearing loss accompanied by tinnitus and gyratoric vertigo, perceptive hearing loss with recruitment in connection with diminished caloric reaction on the diseased side during attacks spontaneous nystagmus

First then there is a possibility to compare the results of histopathological examinations on human temporal bones Thus the findings have consistently been pronounced dilatation of the endolymphatic apparatus particularly in the cochlear duct and the saccule, less pronounced in the utricle and not at all in the semicircular canals, but with herniation of the membranous sacs into the osseous semicircular canals Reissners membrane is bulged up into the scala vestibuli eventually obliterating this or like a hernia pressed through the helicotrema down into the scala tympani Correspondingly, the saccule is seen to obtain much more room in the vestibule than normally, eventually obliterating the perilymphatic space in close contact with the footplate of the stapes It ought to be mentioned, that these changes in English speaking countries are named hydrops, but after Lindsay has demonstrated that this hydrops exists in patients with acoustic disturbances as by Meniere's disease but without vertigo, it might be reasonable to point out the clinical and pathological picture in this type of patient These patients have fluctuating hearing loss of the perceptive type mostly pronounced for deep tones accompanied by recruitment, tinnitus, distortion and discrimination loss In common with Menière's disease is histological finding of hydrops in the cochlear duct, but there is not as the English

name might suggest hydrops in the saccule and the utricle As the last named changes are found alone in Menière's disease Lindsay is inclined to think that changes in vestibulum are responsible for the attacks of vertigo purely mechanically

As the patients with Menière's disease do not die from this but from intercurrent diseases it has lately been criticized that former results from histopathological examinations did not cover changes corresponding to the acute attack, and that lack of changes in vestibular sensory cells might be a consequence of the relatively coarse methods of examination in connection with less satisfactory fixation That an early and good fixation plays a major role for the pathological finding is demonstrated by the publication by Dix & Hallpike in 1952 In a case with particularly good fixation it was possible to demonstrate that the hair cells in the organ of Corti were well preserved on the normal side of a case of Menière's disease, whereas on the diseased side they were clearly degenerated It has to be admitted that generally late fixation and relatively coarse methods of examination makes it hardly possible to control the state of sense cells of the organ of Corti In order to get about these difficulties some investigators in the 1960 es in connection with Cawthorne's labyrinthectomy have examined the removed and freshly fixed lateral membranous semicircular canal along with the ampullary crest Busanny-Caspari and Matzker found on the operation no hydrops of the membranous canal, which corresponds to findings on autoptic material The formalin fixed membranous canal was embedded in paraffin, cut in serial sections and stained with hematoxylin and other staining methods Hyalinisation of the basal membrane, oedema of the wall and vacuoles of the epithelium of the membranous canal was found The authors consider the findings to correspond with the clinical changes but due to the limited biopsy they cannot exclude that labyrinthine hydrops is a consequence of similar functional disturbances in the non accessible part of the labyrinth

Pietrantoni and Iurato said 1960 The state of disease which is known as Menière's syndrome is still a complex symptomatology and an acceptable pathological anatomical base is still lacking Although they admit that changes of the quality and quantity of the endolymph can be of importance they say that the changes causing them are not yet identified and maybe could be of submicroscopical order and consequently only be demonstrated on electronmicroscopical examination on material provided by surgical treatment of the disease However, these preparations can only be compared with normal material from animals On such a comparison they find practically total lack of cilia in the ampullary crest, abnormal inclusion bodies in the sense cells and damage of the mitochondria nerve and sense cells No vascular changes were found directly under the ampullary crest The authors dare not make conclusive remarks on this single case but are inclined to think that the primary changes come from the endolymph as a consequence of toxic or quantitative changes

1961 Litton and Lawrence described a case of Menière's disease where the horizontal semicircular canal and the ampullary part had been examined electronmicroscopically On the background of 10 years electronmicro-

scopical research of normal structures in animals the authors found it obvious to examine the promptly fixed horizontal semicircular canal plus ampullary part moved by destructive labyrinthectomy They compared hereafter the anatomy of the diseased labyrinth along with the findings from studies of normal animals However, they realized that 1) there was no normal human control material, 2) that it could not be excluded that tissue had been damaged on the removal of the membranous labyrinth and 3) finally that even a small delay in fixation to a high extent could alter the cellular structures under the electronic beam Like Pietrantoni and Iurato they found vacuolisation of the cytoplasm in the supporting cells in the ampullary crest, lack of cilia and necrosis of the epithelium in the membranous labyrinth, which they with certainty thought was an antemortem necrosis, and that the process which caused Menière's disease was due to cytotoxity nearly until cell death Hereby they explained the permanent loss of caloric reaction because the neuro epithelium is not able to regenerate

On this background we present two cases of Menière's disease examined in our temporal bone laboratory in a 8 year period amongst about 175 pairs of temporal bones from adults Specimen no I was handed to us by Drs Mygind and Johansen, because it was the wish of the patient (Dida Dederding) to have her temporal bones examined

Her medical record was shortly the following 22 years old first attack of violent gyratoric vertigo and since repeated attacks of vertigo accompanied by feeling of fullness in the head, tinnitus and fluctuating hearing loss of the bass type leading to complete hearing loss on the right side and pronounced loss of hearing on the left side On cold caloric test in 1949 there was no reaction from the right labyrinth 1954 and 1955 admitted to the neurosurgical department for pains in the pelvis During this stay was noted that the patient was deaf apart from small hearing remnants on the left ear, and that there had been no attacks of vertigo the last 10 years She died November 1955 from a malignant tumor of unknown origin in the pelvis

Histological examination of the temporal bones showed normal pneumatization and no inflammation The capsule of the labyrinth showed no abnormalities and particularly there was no otosclerosis This membranous labyrinth showed enormous dilatation of the endolymphatic system except for the membranous semicircular canal, pronounced degeneration of the organ of Corti and the first neuron, most pronounced on the right side, where the disease clinically began No abnormalities were found in the ampullary crests, in the macula of the saccule and the utricle or in the vestibular ganglion

Thus good coincidence was found between the histopathology of the peripheral acoustic organ and the acoustic symptoms, whereas a striking discrepancy was found between the histologically apparently normal vestibular sense organs and the formerly severe vestibular symptoms accompanied by loss of caloric reaction

On autopsy of the brain normal conditions were found, particularly there was no sclerosis of the vessels on the base of the brain Unfortunately no sections

were taken from the oblongate medullary or pons in order to examine the acoustic and vestibular nuclei

The other pair of temporal bones was sent by Dr C C Hansen, University Clinic of Århus under the diagnosis probable congenital bilateral hardness of hearing At the same time Dr Reske Nielsen, Neuropathological Institute, Århus, had taken sections from the brain and the brain stem in order to compare eventual pathological changes in the peripheral and central acoustic apparatus

On microscopy it turned out, however, that both labyrinths presented hydropic changes Due to this one went back in the case history and found out that a Menière's disease on the right ear had developed in the age of 50 At the same time the neuropathologist was stimulated to examine also the central vestibular connections

Moreover the medical history in connection with the histological findings made it likely that the patient at the age of 77 developed hydrops of the left labyrinth in the sense of Lindsay inasmuch rather suddenly severe hearing loss developed on the left ear and on the present histological examination hydrops of the left cochlear duct was found It should be mentioned that the patient during admission at the age of 77 had positive Romberg test, deviation of gait and that she had a cataleptic attack, that the patient 78 years old was treated with hearing aid and then mainly complained of high singing tone in both ears and severe bilateral hardness of hearing, and that the patient 79 years old had paralysis of the right vocal cord and died 81 of pneumonia after some times confusion

The histological examination showed besides the mentioned hydropic changes degenerative changes of the organ of Corti and the first neuron to a higher extent than corresponding to the age and curiously enough most pronounced on the left side, whereas no definite abnormalities were found in the sense cells of the peripheral vestibular apparatus or in the vestibular ganglion

On the neuropathological examination severe degeneration of the brain was found and on comparison with three other brains from the same age group was judged to be more pronounced, particularly in the brainstem One found severe degenerations of acoustic and vestibular nuclei, some degeneration of the vestibular nerves and pronounced degeneration of the marrowsheaths and axons of the acoustic nerves mainly on the left side There was an old subdural hematoma over the right hemisphere and the vessels on the base of the brain were found severely arteriosclerotic but without formation of thrombosis

This last case is of particular interest due to the co operation of the neuro pathologist, also because one visualized the possibility of finding a pathological anatomical cause for the vestibular disturbances in the vestibular nuclei as suggested by Sture Berggren already in the 1930 es In the present case one found degeneration in the acoustic and vestibular nuclei and might be tempted to conclude that Menière s disease is as well a peripheral as a central disease However, it is only a single case and as significance of the neuropathological findings is not quite clear this hypothesis will just be mentioned in connection with the discussion of the pathogenesis

It is difficult to discuss the pathogenesis when neither clinical therapeutic

experiments including surgical treatment nor histopathological examinations have given any clear hint, and when furthermore experiments on animals have not up till now been able to imitate Meniere's disease

It seems obvious that there must be increased pressure in the endolymph which in the final phase becomes permanent Without discussing the cause of this Lawrence & Mc Cabe and Schuknecht & co workers suggested based on histological examinations on temporal bones that rupture of the membranous labyrinth with contamination of endolymph with perilymph was the cause of the episodic nature of Meniere's disease

Lempert has suggested toxic influence by bursting of epithelial vesicles

Perlman and Wullstein have suggested alterations of the electrolytes in the fluids of the labyrinth Apropos this the metabolic examinations on stria vascularis and Reissners membrane performed by Hughes & Chou have the greatest interest They found as expected that the stria vascularis had a high metabolism and found unexpectedly a nearly just as high metabolism in the Reissners membrane This may explain a high K-content in the endolymph and a high Na content in the perilymph Then a diminished blood supply might influence the Reissners membrane to a higher extent than the stria vascularis due to the distribution of the vessels in the cochlea and hereby cause changes of the electrocytes which again might cause dilatation of the cochlear duct decreasing towards the semicircular canals along with alterations of the potentials and hereby diminished hearing These changes may be reversible and may later on become irreversible

When the vestibular apparatus is not involved in all cases it might possibly be due to the fact that the superior part of the labyrinth is phylogenetically the oldest

For a long time it has been supposed that the blood supply of the labyrinth might play a decisive role This is seen in the treatment with vasodilators (Nicotinic acid and Histamin), with block of the sympatic chain in the neck or sympathectomy and treatment with drugs which diminish or are supposed to diminish the viscocity of the blood or the sludging phenomenon (Heparin and low molecular dextrane, the last as infusion) but also treatment with stretching on the cervical columna or operation on the vertebral arteries in the hope to improve insufficiency of the vertebral arteries (and basilar arteries)

In our case no I an insufficiency of the basilar artery due to the normal appearance of the basal vessels of the brain can with an almost certainty be ruled out In case no II, however, it cannot be ruled out, that clinical, neurological and pathological and not the least neuropathological findings can be interpreted as consequences of the pronounced insufficiency of the basilar arteries on arteriosclerotic basis The changes in the brain stem in patient no II might be due to insufficiency on the vertebral artery We have on the other hand had performed arteriography of the vertebral artery in a number of patients with Meniere s disease and up till now found no abnormalities

The same possibility is discussed by Beickert Golding Wood Seymour and Wildhagen Wildhagen examined 1951 a series of patients with Meniere s disease

roentgenologically and found hereby 10 cases in his opinion obviously due to osteochondrosis of the upper cervical column Seymour had a case of Menière's disease caused by insufficiency of the vertebral artery The case was referred by Golding Wood at a meeting about central vertigo in Royal Society of Medicine February 1962 The patient was middle-aged with severe attacks of vertigo hearing loss of perceptive type and sensitivity to noise Furthermore due to general instability insufficiency of the vertebral artery was suspected The patient died after angiography of the vertebral artery and on autopsy one found a very small vertebral artery and a correspondingly small internal auditory artery on one side where also was found endolymphatic hydrops Neither the brain stem nor the opposite ear showed pathological changes

Finally Beickert on the international symposium of Meniere s disease in Padua September 1962 discussed etiology and pathogenesis in Meniere s disease He maintained that the cervical syndrome gives a much more multiple picture than Menière s disease generally does and that the endolymphatic hydrops has no causal connection with disturbances of the hearing and the balance but must be interpreted as a by product to disturbances of metabolism eventually encymatic disturbances with alterations of permability of the membranes

The relationship of the basilar artery insufficiency to Menière s disease must on background be said to be rather uncertain

Much indicates that there is still a long way to go On the other hand undoubtedly further knowledge about the pathology and the pathogenesis of this puzzling disease demands continued careful clinical observations particularly oto neurological examinations attempts with new therapies biochemical examinations examinations with ordinary microscopes and histochemical examinations along with electronmicroscopical examinations but also neuropathological examinations who have so far been considered too little

SUMMARY

Discussing the pathology of Menière s disease it is pointed out that Menière was at least partially right when in 1861 he declared this disease to be labyrinthine origin

Although Menière himself advocated histo pathological examination of temporal bones from such cases this was not done until 1938 by Hallpike & Cairns who demonstrated hydrops of the labyrinth and degeneration of the organ of Corti

Althoughs these findings have been confirmed by many investigators still only little is known about the mechanism of the attacks Newer hypotheses which have been put forward are discussed and particularly the idea of eventual connection between Meniere s disease and vertebral artery insufficiency is mentioned

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MENIÈRE'S DISEASE, SYMPTOMS AND COURCE

By

O Opheim

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Based on a material of 215 patients some data are reported, mainly audiological ones, of special significance for the diagnosis and for the evaluation of therapeutic results

roentgenologically and found hereby 10 cases in his opinion obviously due to osteochondrosis of the upper cervical column. Seymour had a case of Menière's disease caused by insufficiency of the vertebral artery. The case was referred by Golding Wood at a meeting about central vertigo in Royal Society of Medicine, February 1962. The patient was middle-aged with severe attacks of vertigo, hearing loss of perceptive type and sensitivity to noise. Furthermore due to general instability insufficiency of the vertebral artery was suspected. The patient died after angiography of the vertebral artery and on autopsy one found a very small vertebral artery and a correspondingly small internal auditory artery on one side where also was found endolymphatic hydrops. Neither the brain stem nor the opposite ear showed pathological changes.

Finally Beickert on the international symposium of Meniere's disease in Padua, September 1962, discussed etiology and pathogenesis in Meniere's disease. He *maintained that the cervical syndrome gives a much more multiple picture* than Meniere's disease generally does, and that the endolymphatic hydrops has no causal connection with disturbances of the hearing and the balance but must be interpreted as a by product to disturbances of metabolism eventually encymatic disturbances with alterations of permability of the membranes.

The relationship of the basilar artery insufficiency to Meniere's disease must on background be said to be rather uncertain.

Much indicates that there is still a long way to go. On the other hand undoubtedly further knowledge about the pathology and the pathogenesis of this puzzling disease demands *continued careful clinical observations, particularly oto-neurological examinations, attempts with new therapies, biochemical examinations, examinations with ordinary microscopes and histochemical examinations, along with electronmicroscopical examinations, but also neuropathological examinations, who have so far been considered too little.*

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THE PROGNOSIS IN MORBUS MENIÈRE

By

Harry Bjork

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Perhaps more than in any other disease, the clinical course varies from case to case in Morbus Menière (MM) In an attempt to illustrate some factors that may conceivably influence its prognosis, a total of 100 private cases from the period 1954 to mid-1961 have been compiled In 3 patients the disease was bilateral and each of these is here recorded as two cases Only typical cases characterized by tinnitus, attacks of rotatory vertigo with vomiting and a fluctuating hearing impairment were included This selection was made in order to have a reasonably exact basis on which to work I am aware, however, that a number of cases with tinnitus and impaired hearing without vertiginous attacks, and such as are associated with less typical giddiness, are actually Menière cases or belong to the same group Follow up examinations and inquiries for the purpose of this paper were made in about 50 per cent of the cases

Chief attention will be given here to the degree of vertigo and of the resulting hearing impairments in the various age groups and in patients with different types of audiogram Further, the importance of stellate block in the course of the disease will be dealt with

In the age classification, the date of the first vertiginous attack was taken into account since this time is easiest for the patients to define, and since their working capacity is affected by vertigo to a much greater extent than by tinnitus and hearing loss

The degree of severity of the disease has been assessed according to the time (days, months, year, decades) that vertigo in attacks has occurred, and to the frequency, intensity and duration of the attacks

Table I *Mild and severe vertigo in MM, 100 cases classified by age*

Age at first attack of vertigo	Total	Mild cases	Severe cases	(Destructive operation)
34	22	12	10	(3)
35–54	54	34	20	(5)
55–	24	19	5	(1)
Total	100	65	35	(9)

The results in Table I indicate that the severe form of MM occurs most commonly in patients who had their first attack early in life It seems, however, that in evaluating the results a certain caution must be exercised many of these

patients may have been free from vertiginous attacks for long periods, even over ten years, before the onset of a severe phase of illness It is clear that such a course is less likely to develop in the case of patients first affected with vertigo at an advanced age On this view, the differences in Table I do not appear conclusive

Table II *Hearing in affected ear 2—33 years, on an average 8 years, following first attack of vertigo, studied by age groups, 93 cases*

Age at first attack of vertigo	Total	Hearing by whisper metres		
		< 0 5	⋝ 0 5	⋝ 6
34	18	10	8	(6)
35–54	51	25	26	(17)
55–	24	11	13	(4)
Total	93	46	47	(27)

Table II shows the hearing acuity two to 33 years, on an average 8 years, after the first vertiginous attack, and the case material is divided into three age groups At the time most of the patients had already definitely or temporarily conquered the active stage of the disease The analysis of hearing should, of course, preferably have been based on audiometric studies, but a sufficient number of audiograms from the late stage were not available As the grouping was made fairly roughly, the chances of faulty conclusions should not be particularly big even though based only on tests by whispered voice

It is seen from Table II that hearing for whisper in approximately half of the cases was restored to 0 5 m or more and that, in 27 out of the 93 cases, it reached or exceeded the 6 m limit. What is interesting here is that no statistically significant difference appears between the various age groups in regard to restoration of hearing This is of particular importance as far as concerns cases with different types of audiogram, which will be dealt with later on in this paper

Naturally enough, the so-called severe cases resulted in more profound hearing loss than the mild cases However, some of the former showed surprisingly good restoration of hearing and in two the hearing for whisper reached 6 m in spite of the disease, with frequent major attacks, having lasted long, for years even It therefore seems that one should be cautious in forecasting the development of hearing especially as long as greater fluctuations can be observed on repetition of examinations

It is well known that pure tone audiograms of different perceptive types occur in MM A rising curve has been considered characteristic of the early phase of the disease The present case material, however, includes 9 cases in which a

curve of rising type was obtained after years of illness and 4 of these cases were in the group "severe cases Yet there have been cases in which the audiogram, initially of the rising type, later changed in character

Table III *Types of pure tone audiogram in MM in different age groups, 80 cases*

Age at first attack of vertigo	Total	Audiogram		
		Rising	Horizontal	Falling
–34	19	14	2	3
35–54	45	17	10	18
55–	16	4	5	7
Total	80	35	17	28

Table III is based on only 80 cases because, in the remaining, the audiogram represented none of the three types It is worth noticing that a rising curve was recorded in as many as 35 of the 80 cases which may perhaps be attributed to the case material consisting of only typical cases of MM

The age distribution of the cases with different types of audiogram arouses interest It would be expected of course that a falling curve is more common among older patients, since the high tone loss associated with advanced age cannot be entirely eliminated. The table shows that all three types of audiogram occur in each age group, but that the rising curve is in relative terms more common in those whose attacks started at an early age It should be noted, however, that 17 of the 35 rising curves occurred in the age group 35—54 years, and four occurred in patients aged 55 or over

Table IV *Mild and severe vertigo in MM, 80 cases classified by type of pure tone audiogram*

Audiogram at first examination	Total	Mild cases	Severe cases
Rising	35	24	11
Horizontal	17	10	7
Falling	28	16	12
Total	80	50	30

Table IV illustrates the distribution of mild an severe cases of MM into the three audiometric groups As will be seen, mild disease was more frequent in cases with a rising type of audiogram, but the difference is not statistically fully significant taking into consideration the relatively limited number of cases The differences must rather be regarded as uncertain

PATHOLOGICAL STUDIES IN PERCEPTIVE DEAFNESS

A PATIENT WITH HYDROPS OF THE LABYRINTH

By

C C *Hansen* and *Edith Reske Nielsen*

From the Department of Otolaryngology (Head Prof H. C. Andersen) and the Neuropathological Laboratory (Leader E Reske Nielsen) of the Institute of Pathology Aarhus Kommunehospital University of Aarhus Denmark

During the study of a collected material consisting of brains with hearing organs from patients whose hearing was known, we observed bilateral hydrops of the labyrinth in one of the patients

As far as we know, pathological studies on brains from patients with confirmed labyrinthine hydrops have not previously been published Accordingly, we intend, on the basis of a comparison of our own observations and the known pathological and neurological symptoms in Menière's disease, to discuss its aetiology

Menière studied both the temporal bone and the brain in the patient he described in 1848 and 1861 This patient revealed changes in the vestibular part of the labyrinth, but not in the acoustic part, and no abnormalities were found in the central nervous system (Atkinson 1961 (4))

At the present time, Menière's disease is defined clinically as a combination of impaired hearing, tinnitus and vertigo In the early phase of the disease, the impairment of hearing involves only the low frequencies It fluctuates during the attacks, but later it becomes constant and spreads towards the high frequencies The tinnitus is usually high pitched and constant, but in relation to the attacks of vertigo it becomes deeper and roaring Between the attacks, the vertigo may be present as a feeling of unsteadiness, but during the crises it becomes gyratory and is accompanied by nausea and vomiting

The aetiology and pathogenesis of Menière's disease are discussed below on the basis of previously reported histopathological and clinical observations

A CHANGES IN THE EPITHELIAL PART OF THE LABYRINTH

1 *Labyrinthine Hydrops*

The most conspicuous pathological finding in the labyrinth is a dilatation of the endolymphatic duct (hydrops) through all the cochlear coils, possibly also involving the saccule and utricle Labyrinthine hydrops was described for the first time by Hallpike and Cairns (1938 (19)) together with degenerative changes in the organ of Corti

In the same year, Mygind and Dederding (1938 (34)) suggested that the fluctuations in hearing experienced during the attacks were referable to changes

in the pressure in the endolymphatic system caused by the hydrops The changes in the threshold during attacks occur only for the low frequencies (Lindsay 1960 (27)) Lindsay reported that 50 % of his patients had a symmetrical hearing loss for high tones which did not change during the attacks, while the hearing was impaired within the range from 250 to 1000 cps in the affected ear In experiments with overpressure on a model of the cochlea, Tonndorf (1957) (46)) believed to be able to explain the hearing loss for low tones, the diplacusis and the lowering of the threshold for aural harmonics on the basis of changes in the physical properties of the model during increased tension in its "scala media" The rigidity of the basilar membrane varies exponentially across the membrane (Békésy 1956 (7)) and thus facilitates the formation of migrating waves across it. It may be thought that increased distension of the basilar membrane caused by [illegible] vibrations and

[illegible] to change the

[illegible] h the greatest

changes in the physical properties of the basilar membrane have occurred. The cochlear microphonic potential, which, inter alia, reflects the state of the hair cells, changes in parallel with the pressure in the scala vestibuli (McCabe et al 1961 (31)) McCabe et al did not succeed in creating an increased pressure in the scala media of the experimental animals (guinea pigs), and their experiments failed to explain why the threshold changes occurred only in the apical coil of the cochlea, in which low frequencies are perceived

Although it is believed that most of the symptoms of Menière's disease can be traced back to labyrinthine hydrops, it is difficult to explain the attacks which suddenly occur without being accompanied by parallel changes in the labyrinth In addition, the patients feel well between the attacks even though the hydrops persists (Podvinec et al 1963 (38))

2 *Damage of the Organ of Corti*

The tectorial membrane is, because of the hydrops, squeezed down over the other structures of the organ of Corti

It is difficult to evaluate the histopathological changes in the hair cells Schuknecht (1953 (42)) observed only slight changes in the organ of Corti and its hair cells in the ears he studied Nevertheless he found that it was likely that the hearing impairment was due to a change in the hair cells For example, he reported that it was possible to produce a mild hearing loss in experimental animals without causing histologically demonstrable changes in the supporting structures or the hair cells of the organ of Corti Schuknecht assumed that the effect on the hair cells was most pronounced in the apical coil of the cochlea (i e, corresponding to the hearing loss for low frequencies) In agreement with this, Kristensen (1961 (24)) found that the histologically demonstrable changes were most pronounced in this area of the cochlea

It might be thought that the epithelial changes in the apical coil were secondary to those in the neural elements in the same area In a patient with Menière's

disease, Lindsay and Schulthess (1958 (28)) observed a striking reduction in the number of nerve fibres and ganglion cells in the apical coil without any changes in the epithelial elements in the same area In this case, the damage of the first neurone must have developed before the degeneration of the epithelial elements became visible

On the basis of clinical observations, Dix, Hallpike and Hood (1948 (15)) reported that recruitment is associated with Meniere's disease Thus, Hood (1961 (23)) found recruitment in all the cases he had personally observed Pathologically, recruitment indicates impaired function of the inner hair cells of the organ of Corti, but not of the cochlear nerve fibres

It thus seems as if, in Menière's disease, the damage of the hair cells of the organ of Corti is most pronounced in the apical coil This damage is partially caused by the hydrops, but may also be secondary to changes in the neural elements of the cochlea

3 Other Epithelial Elements of the Cochlear Part of the Labyrinth

Specific changes in the stria vascularis have not been described Rollin (1940 (39)) found a normal stria vascularis in a patient with enormous hydrops and pronounced loss of nerve fibres in the apical coil of the cochlea Similar observations have been made by Kristensen (1961 (24)) and others

No authors have described structural changes in the basilar or tectorial membrane or in the supporting structures of the cochlea

In association with hydrops through the cochlear coils, several investigators have observed dilatation of the saccule, yet without co existing changes in its macula acustica (Rollin 1940 (39)), Lindsay 1960 (27)), Kristensen 1961 (24))

4 Changes in the Epithelial Part of the Vestibular Apparatus

Endolymphatic hydrops does not seem to extend to the vestibular part of the labyrinth (Hallpike and Cairns 1938 (19)), Rollin 1940 (39)), Lindsay 1960 (27) and others) Kristensen (1961 (24)) observed considerable dilatation of the utricle in a patient with enormous hydrops through the cochlea and saccule, whereas the semicircular ducts were undilated From extensive literature studies Aubry and Pialoux (1957 (3)) concluded that dizziness during attacks is caused either by the intralabyrinthic pressure, angioneurotic disturbances or other vascular disorders Lindsay (1960 (27)) reported that the vestibular disturbances during attacks could best be explained on a mechanical basis, viz as a disturbance of the ampullary mechanism in one or more of the ampullae during hydrops Evidence against this assumption is provided by the fact that Busanny Caspari and Matzker (1960 (8)) did not find any hydrops in a semicircular duct which had been removed while the patient concerned had a violent Meniere attack in that ear Histological examination of the removed length of the lateral semicircular duct revealed hyalinisation of the basilar membrane in the semicircular duct and oedema of the connective tissue with an increased number of connective-tissue cells mainly in the perilymphatic spaces Under the electron microscope Pietrantoni and Iurato (1960 (37)) also studied the lateral semicircular duct after laby

rinthectomy The severest lesions were found in the surfaces (cilia and cuticular border) of the sensory epithelium, while the system in which the impulses are transformed (mitochondria and cyto neural junctions) was less damaged There was no vascular lesions The fact that Lindsay (1960 (27)) found normal vestibular reactions in patients with far advanced hydrops weighs against the assumption that *the surface lesions described are solely responsible for the impaired* vestibular function Incidentally, a typical finding is the conspicuous discrepancy between the histologically normal vestibular sensory organs and the severe impairment of vestibular function (Kristensen 1962 (25))

B CHANGES IN THE NEUROGENIC PART OF THE LABYRINTH

1. *Acoustic Part (First Neurone of the Acoustic Pathways)*

Several authors have in patients with Meniere's disease observed significant degeneration of the neural elements of the apical coil of the cochlea, corresponding to the hearing loss for low frequencies (Rollin 1940 (39)), Lindsay and Schulthess 1958 (28), Lindsay 1960 (27), Kristensen 1961 (24)) Lindsay (1960 (27)) did not find appreciable degeneration of the nerve elements in the early stages of the disease, but only in more advanced cases As previously mentioned, Lindsay and Schulthess (1958 (28)) observed in one patient considerable reduction in the number of nerve fibres and ganglion cells belonging to the apical coil, but as contrasted with this a nearly normal number of hair cells in the area in spite of the labyrinthine hydrops of the patients In advanced cases, the degeneration of nerve fibres leads to damage of the sensory cells of the organ of Corti, whereas the spiral ganglion may be perfectly normal in spite of advanced degeneration of the hair cells

In experiments on cats Schuknecht and Neff (1952 (43)) demonstrated that the hearing loss produced by destructions in the apical coil is identical with that occurring in the initial stage of Meniere's disease On the other hand, destruction of the basal coil resulted in a *steep hearing loss for high tones The shape of the* audiogram in Meniere's disease (especially during the attacks) shows great similarity to that for the hearing loss produced by destructions in the apical coil, either by injury inflicted on the hair cells or the neural elements

Dandy (1937 (12)) reported that, in operations in which section of the cochlear nerve was performed, this nerve showed severe macroscopic changes in its peripheral course through the internal auditory meatus In 20 % of the patients, a large artery (one of the branches of the superior inferior cerebellar artery) rested against the nerve, for which reason Dandy expressed the view that changes in the nerve itself were one of the causes of the impaired hearing and tinnitus in Meniere's disease

2 *Vestibular Part (First Neurone of the Vestibular Pathways)*

So far no changes in the vestibular ganglion or the nerve fibres belonging to the first neurone of the vestibular paths have been reported In the patient de-

scribed by Kristensen (1961 (24)) the vestibular ganglion was normal The Nissl granules seemed even to be more well-preserved than in sections from normal ears The galvanic reaction which is assumed to be excited from the vestibular ganglion was reported to be normal The discrepancy between the often severe symptoms of impaired vestibular function and the histologically normal findings in the first neurone is a striking feature

C. CHANGES IN THE HIGHER COCHLEAR AND VESTIBULAR NEURONES OF THE CENTRAL NERVOUS SYSTEM

1 *As the Cause of Labyrinthine Hydrops*

It is believed that labyrinthine hydrops may occur as a concequence of changes in the labyrinthine vessels (vasomotor lability, allergy) or in the chemical composition of the endolymph

Just as there is a cerebral mechanism of protection which ensures a constant pressure in the cerebrovascular system, it is likely that there is a similar mechanism ensuring a constant pressure in the labyrinth (Aubry and Pialoux 1957 (3)) It is possible that pathological conditions around the centre for the regulation of the latter mechanism (which is assumed to be situated in the hypothalamus) may give rise to disturbances in the peripheral vessels, for example, in the labyrinth, eye or other regions in the endocranium Dederding (1929 (13)) published three cases of Menière's disease associated with Quincke's oedema of the subcutaneous tissue Dederding and Mygind (1931 (14)) advanced the theory that Menière's syndrome should be caused by extravasation of fluid into the intralabyrinthine tissue They reported good results of treatment with a salt-free diet and reduced fluid intake Cases of Menière's disease associated with glaucoma were published by Godtfredsen (1949 (16)) However, Henin Robert (1957 (21)), in 83 patients with glaucoma, saw Menière's disease only in one case Hilger (1950 (22)) likewise compared endolymphatic hydrops with the intra ocular hypertension in the presence of glaucoma Menière's disease has also been discussed together with migraine (Sorensen 1959 (45)), changes in the conjunctival vessels (Naito 1962 (35)) and extensive vascular changes causing transitory damage to the areas supplied by the trigeminal and, possibly, facial nerves evidenced by Bell's palsy (Podvinec et al 1961 (38))

Wever and Lawrence (1952 (47)) suggested that changes in the composition of the endolymph might give rise to hydrops of the labyrinth Apart from a somewhat higher content of protein, the chemical composition of the perilymph is roughly the same as that of the cerebrospinal fluid (Smith, Lowry and Wu 1954 (44)), Citron and Exley (1957 (9)), while the composition of the endolymph is more like that of the intracellular fluid with a low sodium and a high potassium content Accordingly, the endolymph cannot be an ultrafiltrate from the blood, but must be formed at the result of an active secretion in the labyrinth and is subject to cerebral regulation probably by the centre regulating water and salt metabolism, which is situated in the diencephalon (hypothalamus) According to Altman (1955 (1)) and Maspetiol (1962 (30)) this regulation is

effected through the sympathetic and parasympathetic systems Neurophysiologically, a connexion can be demonstrated between the reticular formation and the hypothalamus

The composition of the blood plasma fluctuates during Menière's attacks Clayton et al (1962 (10)) demonstrated in a child increased serum concentrations of potassium, calcium and magnesium during attacks (whereas the potassium content of the cerebrospinal fluid was not simultaneously increased)

In view of the changes observed in the vascular conditions and in water and salt metabolism in affected patients it is reasonable to assume that Menière's disease must be regarded as a disturbance, inter alia, in the diencephalic mechanism of regulation, and it has other features in common with other diseases of the vegetative nervous system, e g its dependence on exposure to stress The diencephalic pathogenesis of Menière s disease allows numerous exogenic and endogenic factors to become significant trigger stimuli (Rossberg 1960 (40))

2 *As the Cause of Impaired Hearing*

A hearing loss for low frequencies as in Menière's disease, may in addition to degeneration of the apical coil of the cochlea be referable to pathological processes in the brain stem Parker (1962 (36)) found it "rightly argued" that sensory lesions, such as Menière's disease, vascular thrombosis and other lesions of the brain stem, many produce a hearing loss in the low frequency range, in particular, in the presence of unilateral perceptive hearing loss in the low-frequency range the examiner should be on the look-out for a central neurogenic process These observations are supported, for example, by Gravendeel and Plomp (19[illegible] (17)), who in 16 out of 23 patients with hearing impairments in the low-[illegible]quency range found electro-encephalographic abnormalities ("mostly of [illegible] nature of diffuse or isolated paroxysmal activity of an epileptiform charac[illegible]

Perceptive deafness in the low-frequency range has been seen after [illegible]taxis cautery in the mesencephalon (Saltzmann 1952 (41)) McConnell (19[illegible] (32)) and Batson and McConnell (1958 (6)) observed a correlation betwe[illegible]

[illegible]

several cases of elective hearing loss for low tones of the perceptive type [illegible] tients with tumours of the mesencephalon and pons, but never in les[illegible] hemispheres

Perceptive hearing loss for low tones may thus to some extent be caused [illegible] lesions of the brain stem

The high pitched tinnitus in Menière's disease may also be caused by a [illegible] lesion In 20 of the patients in whom Dandy performed section of [illegible] lear and vestibular parts of the eighth nerve Crowe (1937 (11)) [illegible] only eight of the patients were completely freed of the tinnitus [illegible] the tinnitus remained unchanged, and it was aggravated in one [illegible] able that any cochlear lesion should give rise to tinnitus after [illegible] of the eighth nerve

[illegible]

3 *As the Cause of Vestibular Symptoms*

Montandon (1959 (33)) performed electro nystagmographic studies in 15 patients with Menière's disease All the patients revealed signs of hypo-irritability in the peripheral part of the vestibular apparatus, but the nystagmus had a small amplitude, was of the pendular type, and its intensity was independent of that of the stimulus, all these observations are suggestive of vestibular symptoms caused by lesions of the central nervous system In this connexion, Montandon mentioned some recent experiments by Lachmann in which he demonstrated the existence of a meso diencephalic nystagmogenic centre regulating the vestibular mechanism Aschan and Stahle (1957 (2)) and Maspetiol et al (1961 (29)) likewise found that some elements of the nystagmus could be explained only on the basis of a central aetiology

4 *As the Cause of Other Neurological Symptoms*

Crowe (1937 (11)) observed loss of consciousness, transient diplopia and, some times, disturbances in the corneal sensibility on the affected side in patients with Menière's disease Homolateral trigeminal paralysis and endolymphatic hydrops were described by Podvinec et al (1961 (38)) in nine out of 18 patients with Menière's disease who were subjected to a close study The same authors reported a case of Bell s palsy which occurred simultaneously with the first attack of Menière's disease Finally, it should be mentioned that Greiner et al (1954 (18)) described a patient with unilateral Menière s disease which occurred in association with syringomyelia

The review of the accessible literature thus seems to show that the causes of Menière's disease should be sought not only in endolymphatic hydrops, but may also be attributable to pathological changes in the brain stem

CASE REPORT

The patient was a woman, born Oct 14 1877, who died at the age of 83 years on Jan 29, 1961 Apart from chronic rheumatoid arthritis and achlorhydria, she had always been in good health At the age of 50, increasing tinnitus and decreasing hearing in the right ear developed, accompanied by episodes of vertigo for which reason she was admitted to the Ear Clinic (Head E Lange) of Sct Joseph's Hospital, Aarhus Nothing in the past history could explain the impaired hearing In the right ear, a whisper could be heard only ad aurem (a a) while the hearing in the left ear was normal At a check up examination later in the same year (patient now aged 51) only slight non paroxysmal vertigo was present but there was constant tinnitus, and the "deafness in the right ear remained unchanged

At the age of 60 i e 10 years later, the patient experienced another period with severe paroxysmal vertigo At the age of 77 i e 27 years after the first attacks the patient was re admitted to Sct Joseph's Hospital because the frequency of episodic vertigo had again increased The patient now also complained of rapidly decreasing hearing in the left ear and of distorsion of all sounds

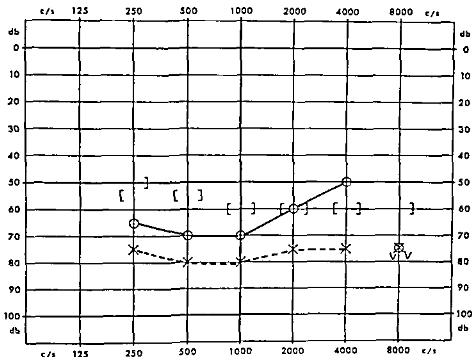


Fig 1 Pure tone audiogram (from the State Hearing Rehabilitation Centre, Århus)

Hearing tests whisphered voice R/L = a a /0 50 m, conversational voice R/L = a a./3—4 m Tests for vestibular function performed by irrigation with 50 ml tap water below 10° C showed brief and weak reactions in both ears, which the examiner described as a very severe impairment of the function Further examinations showed a positive Romberg sign and constant deviation to the left during walking with closed eyes During the hospital stay, the patient had a cataleptic attack Achlorhydria was disclosed and treated with HCl tablets It is reported that achlorhydria has very often been observed in association with Menière's disease in Sct Joseph's Hospital, and that the treatment with HCl tablets results in an improvement of both the gastric disorder and Menière's disease (26)

At the age of 78, the patient consulted the State Hearing Rehabilitation Centre, Aarhus, and was given a hearing aid At that time, the complaints were only non gyratory vertigo, a high pitched singing sound in both ears and severe bilateral impairment of hearing

(Fig 1) The audiogram showed severe perceptive hearing loss for both low and high frequencies, especially in the left ear Rinne's test was positive on both sides Speech audiometry revealed a discriminative threshold of 50 in the left ear, discrimination loss 90 % The patient did not derive any benefit from the hearing aid The patient could hear with the right ear, but she was unable to perceive the words and figures read aloud to her, for which reason a hearing aid was not attempted

At the age of 79, the patient consulted Dr Lange because of indeterminate

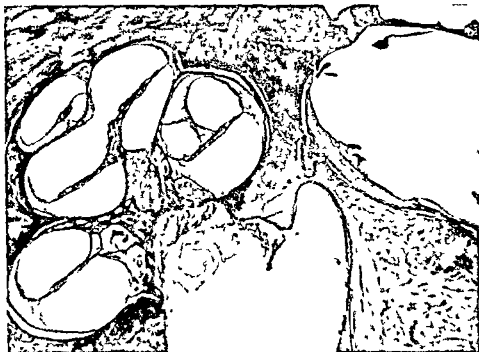


Fig 2. Right cochlea Notice the endolymphatic hydrops and saccular dilatation (Haematoxylineosine)

complaints. Impaired mobility of the right vocal cord was disclosed. Oesophagoscopy did not show oesophageal abnormalities, i. e. the examination failed to reveal any peripheral explanation of the paresis. At the age of 83, the patient was admitted to the Infirmary (Head: E. Scherwin, M.D.) of the local Home for the Aged after having been found lying on the floor in her home. She was confused and delirious on admission. Death from pneumonia occurred one month later.

Autopsy revealed thrombosis of the left pulmonary artery and infarction of the lower lobe of the left lung, left-sided pneumonia and severe atrophy and arteriosclerosis of the organs. Nothing was revealed, which could explain the paresis of the right vocal cord.

HISTOLOGICAL STUDIES

Both temporal bones were prepared for histological studies in the laboratory of the Department of Otolaryngology (Head: Professor H. K. Kristensen, M.D.), Rigshospitalet, Copenhagen.

Right Temporal Bone

The *middle ear* was normal.

The *cochlea* showed pronounced hydrops through all the coils The vestibular membrane was tense and adherent, in some places, to the wall of the scala vestibuli. The tectorial membrane was pressed down over the organ of Corti, which was apparently normal (Fig. 2).

The *vestibular membrane* seemed to be atrophic in some areas, while in other proliferation of the epithelial cells was observed On the other hand, there was no thickening of the connective tissue, and no inflammatory cells were present

The *basilar membrane* was normal

The *stria vascularis* was normal in particular, the vessel walls were not thickened There was no reduplication of the endotheliomatous basilar membrane *Proliferation of the endothelium was absent There were no thrombi*, and the lumina were not narrowed Similar, normal conditions were observed in the vessels of the modiolus

The *saccule* was enormously dilated, its membrane resting against the inner side of the footplate of the stapes Some dilatation of the *utricle* was also observed, whereas the semicircular ducts were undilated The epithelial elements were otherwise normal

Neural elements (first neurone) — The *cochlear ganglion* showed appreciable loss of ganglion cells in the basal coil, but only slight loss of cells in the middle and apical coils Some of the preserved ganglion cells showed vacuolation with abnormal peripheral displacement of the nucleus The Nissl substance could not be definitely assessed There were a few shrunken cells The capsule cells and Schwann cells did not reveal any proliferation

The *acoustic nerve* showed considerable loss of myelin sheaths and axis cylinders, those which remained were swollen, fragmented and of unequal calibre, although these abnormalities were less pronounced in the axons (In view of the conditions of the axons and myelin sheaths and the clinical picture, i e severe hearing loss, it is surprising that so many ganglion cells were preserved)

The Scarpa ganglion was not included in the sections from the right temporal bone, but the vestibular nerve was present in several sections and showed only slight degeneration

Left Temporal Bone

The *middle ear* was normal

The *cochlea* (epithelial part) showed less hydrops than on the right side The vestibular membrane was very tense, but did not adhere to the wall of the scala vestibuli (Fig 3)

The *tectorial, basilar* and *vestibular membranes* and the *stria vascularis* were as on the right side

The *saccule* and *utricle* did not show any dilatation, nor were any changes observed in the semicircular ducts The epithelial elements were otherwise normal

Neural elements (first neurone) — As compared with the right side, the cochlear ganglion showed largely fewer ganglion cells, but the same degree of degeneration in the remaining cells, although most pronounced basally

The *acoustic nerve* showed almost complete loss of myelin sheaths and axis cylinders and severe degeneration of the scarce remnants in the central glial part In addition, massive accumulation of corpora amylacea was observed The

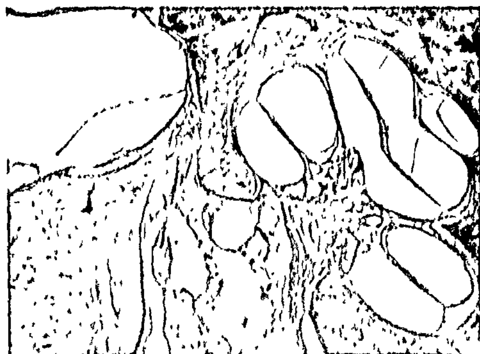


Fig. 3. Left cochlea with endolymphatic hydrops, which on this side is less pronounced. There is no saccular dilatation. (Haematoxylin-eosin.)

peripheral part was markedly degenerated, but the loss of myelin sheaths and axis cylinders was relatively slight. There were no reactive changes and no inflammatory cells (Fig. 4).

The vestibular part was well preserved (almost normal). The Scarpa ganglion showed no loss of cells and only slight degenerative changes (Fig. 5).

Cerebrum

Macroscopic appearance. — After fixation, the brain weighed 1300 g. The brain was dissected free together with the dura. Removal of the dura revealed a large subdural haematoma over the anterior part of the right hemisphere, extending from the frontal pole backwards to the central sulcus. The haematoma was so old that membranes has formed. Its maximum thickness was 6 mm. The haematoma had formed an impression on the surface of the brain. The starting point of the haemorrhage could not be detected. The brain was oedematous with conus formation on the cerebellum and pressure grooves on both unci. It was pale, and diffuse cortical atrophy was observed. The leptomeninges were moderately blurred. There were no acute exudates. The vessels of the base of the brain showed severe atherosclerotic changes with dilatation and numerous atheromatous plaques and narrowing of the lumina, but thrombi were absent. The changes were of the same nature in all vessels and extended to the peripheral ramifications.

A central block of the cerebrum, brain stem and cerebellum was cut out in



Fig 4 Longitudinal section through the left vestibular nerve which is placed in the upper left corner of the picture and which is normal and (below to the right) the acoustic nerve with severe degenerative alterations (Bodian)



Fig 5 Left Scarpae's ganglion with normal ganglion cells and axons (Bodian.)

order to study the course of the acoustic pathways and the pathological changes The block was bounded by the chiasm anteriorly, the gyri hippocampi laterally, and the cerebellum posteriorly, and it was cut into coronal sections Grossly, the brain stem did not present any abnormal features The corpus geniculatum mediale was smaller on the left than on the right side The fourth ventricle was normal, the aquaduct was not dilated In the cerebellum, the right brachium conjunctivum showed a fresh haemorrhage measuring 2 mm in diameter The third ventricle was narrow The corpus striatum, nucleus caudatus and thalamus were grossly normal

The remaining part of the brain was cut into coronal sections The pattern was normal There were no haemorrhages, cysts or fresh malacias The ventricular system was slightly compressed The walls were shining and reflecting

The *acoustic tracts* were studied in the following sections

1 The junction between the pons and medulla oblongata with both acoustic nerves
2 The pons with the trigeminal nerve
3 The mesencephalon with the inferior colliculus
4 The upper part of the mesencephalon with the corpus geniculatum mediale
5 The right and left temporal lobes with the superior gyrus and the transverse gyri

These sections were stained with haematoxylin eosin, toluidine blue, gallocyanin chromalum (Einarson), Mahon, van Gieson, periodic acid Schiff (PAS) and Davenport methods

HISTOLOGICAL EXAMINATION OF THE BRAIN

Central Acoustic Pathways

1 Both *acoustic nerves* showed pronounced loss and severe degeneration of myelin sheaths and axis cylinders, but the changes were most conspicuous on the left side The myelin sheaths were fragmented and of a beaded appearance, while *the axis cylinders were corkscrew like and interrupted Some were very thin,* while others were swollen No normal nerve fibres were seen Corpora amylacea had accumulated everywhere in the nerves (Fig 6) Severe degeneration of the ventral and the dorsal cochlear nucleus was seen on both sides The ganglion cells showed a varying degree og degenerative changes Some cells were ghostlike with vacuolated cytoplasm and a few chromatin flakes in the periphery The processes were thickened and distinctly visible for considerable distances into the tissue Other cells were of a rounded shape with eccentrically placed nucleus and nucleolus The cytoplasm contained accumulations of granules which assumed a faint pale yellow colour on staining with gallocyanin-chromalum The Nissl substance was displaced towards the periphery and had accumulated into coarse lumps Finally, shrunken ganglion cells with dense small nuclei and sparse amounts of cytoplasm were present. Satellitosis and astrocytosis were absent, whereas the micro-glial cells had large, deformed sometimes hourglass shaped,

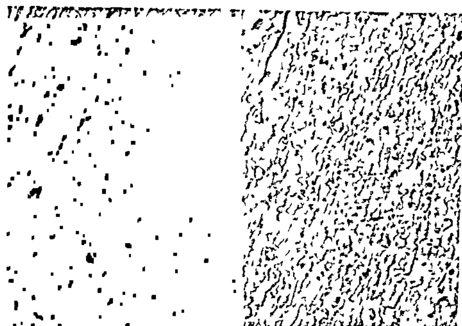


Fig 6 Left acoustic nerve (glia part) with enormous outfall and very severe degeneration. Notice the fragmented axons with blister-like swellings (Davenport)



Fig 7. Left ventral cochlear nucleus The cytoplasm is filled by tiny PAS-positive granules, the nuclei show swelling, are displaced and, in one case, even leaving the cell (Gallocyanin chromalum)

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Fig 6 Left acoustic nerve (glia part) with enormous outfall and very severe degeneration. Notice the fragmented axons with blister like swellings (Davenport.)

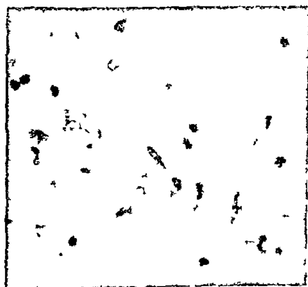


Fig 7 Left ventral cochlear nucleus The cytoplasm is filled by tiny PAS-positive granules, the nuclei show swelling are displaced and in one case even leaving the cell. (Gallocyanin chromalum)

nuclei as if they were in amitotic cell division Accumulations of PAS positive granules were observed in the cytoplasm (Fig 7)

2 The *pons* did not reveal any elective degeneration of the corpus trapezoideum or lateral lemniscus Apart from the brachium pontis, the white matter showed uniform, diffuse degeneration The second neurone from the dorsal cochlear nucleus emitted axons along the floor of the fourth ventricle These axons were markedly swollen and, in some places, fragmented and of unequal calibre Similar axons from the ventral cochlear nucleus passed into this band in the floor of the fourth ventricle

3 The *mesencephalon* showed uniform degenerative changes in the inferior colliculus on both sides This degeneration was of the same intensity as the other changes seen in this part of the brain stem Only a few ganglion cells were surrounded by *satellites* *The microglia showed conditions as described above* PAS-positive granules were present in the ganglion cells

4 The *corpus geniculatum mediale* revealed massive accumulation of corpora amylacea Slight loss of ganglion cells was noted, and the remaining cells showed the same degenerative changes as those described above The cytoplasm was studded with yellow granules which showed a positive reaction on PAS staining

5 The *cortex* of both temporal lobes revealed subpial gliosis, and the glial cells contained PAS positive granules The ganglion cells showed degenerative changes of the aforementioned character and contained varying amounts of PAS positive granules Similar conditions were also seen in the glial cells and phagocytes along the vessels (Fig 8) There were enormous loss and severe degeneration of both myelin sheaths and axis cylinders, but no astrocytosis or inflammation Interspaced between the myelin sheaths there were phagocytes with PAS positive material (Fig 9 and 10)

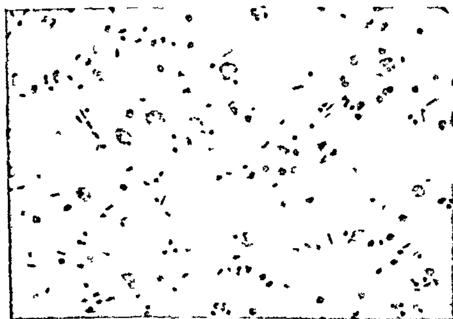


Fig 8 Right temporal cortex There are focal loss and degeneration of the cells



Fig 9 White substance of the right temporal lobe Severe degeneration of the myeline sheaths is visible (Mahon.)

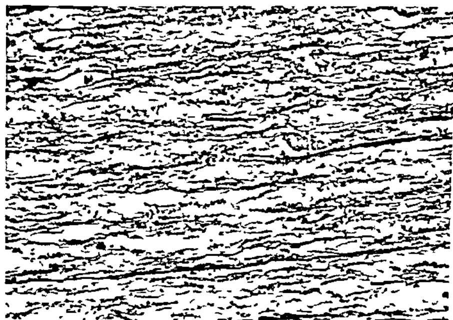


Fig 10 White substance of the right temporal lobe The axis-cylinders show severe pathological changes (Davenport)

Central Vestibular Pathways

The point of entry of the vestibular nerve could be seen on both sides Degeneration was manifested by swollen and fragmented myelin sheaths and axis cylinders of unequal calibre The further course of the nerves could not with certainty be followed between the restiform body and the nucleus tractus spinalis of the trigeminal nerve On the other hand, the lateral and medial nuclei of the vestibular nerve were distinctly visible Enormous loss and severe degeneration of the ganglion cells were seen on both sides (Fig 11 and 12) Mahon staining showed practically no remnants of the myelin sheaths of the medial vestibular nucleus on the left side, whereas degenerated myelin sheaths were present in the same nucleus on the right side The axis cylinders in this area were also more severely affected on the left than on the right side It should also be noted that there was severe diffuse degeneration of both nuclei and pathways in the entire brain stem, but the changes seemed to be severest in the vestibular parts of the nuclei of the cranial nerves Like the two nuclei just described, the superior vestibular nucleus showed loss and degeneration of the ganglion cells

Vascular Changes

The capillaries of the brain stem and cerebrum were thickened, the arterioles had thickened hyaline walls and narrowed lumina, but thrombi were absent The large vessels, both arteries and veins, in the white matter showed increased width of the adventitia and some fibrosis in the other layers The lumina seemed to be of normal width, without thrombi The dilated perivascular spaces contained phagocytes with pigment and PAS positive granules

The *leptomeninges* showed fibrosis and some infiltration by lymphocytes and macrophages with PAS positive granules The branches from the circle of Willis was the seat of moderate atherosclerotic changes, but neither fresh nor old thrombi were present

DISCUSSION

Acoustic System

Clinically, the patient revealed complete loss of hearing for the upper part of the high frequency range in both ears, while the hearing impairment for 4000 cps and lower frequencies was most pronounced in the left ear

Endolympathic hydrops was present in both ears most pronounced on the right side, where the dilatation extended into the saccule

If the hearing loss for low tones had exclusively been due to hydrops, it should have been expected that the hearing loss would have been severest on the right side, where the hydrops was most pronounced and not on the left as was actually observed

The pathological changes in the spiral ganglion and the peripheral part of the acoustic nerve were most pronounced on the left side where the hearing impairment was severest Accordingly there seems to be a correlation between the

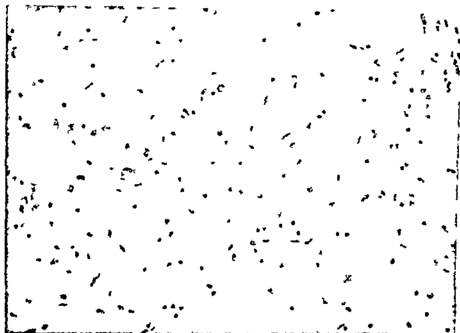


Fig 11 Right lateral vestibular nucleus There are outfall degenerative alterations and gliosis (Gallocyanin chromalum)

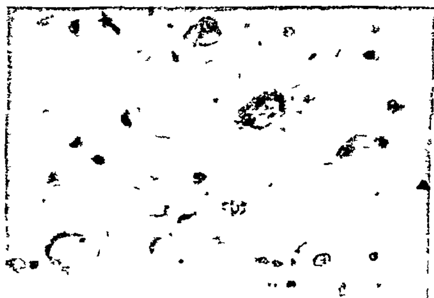


Fig 12 High magnification of No 11 The degeneration is convincing

severity of the hearing impairment and that of the degeneration of the spiral ganglions and the peripheral part of the acoustic nerves.

A comparison of the pathological findings in the temporal bones, especially in the organ of Corti and the spiral ganglion, with the changes observed in the auditory tracts and nuclei of the central nervous system seems to show that the severest degeneration had occurred in the brain stem and the auditory centres, especially in the glial part of the acoustic nerves and in the white matter of the temporal lobes. In view of these observations, it must be reasonable to conclude that the hearing loss revealed in the patient was mainly of central origin.

It seems as if the hearing loss for low tones which is usually considered to be referable to Menière's disease, was not exclusively caused by the endolympathic hydrops, but was also partially attributable to changes in the central nervous system.

The symmetrical hearing loss for high tones observed in the patient may perhaps be explained by diffuse degeneration of the brain as suggested in a paper read by us before a meeting of the Danish Society of Neurology in May 1963.

Vestibular System

Clinically, the patient showed markedly reduced caloric response in both ears, attacks of vertigo and a feeling of unsteadiness during gait.

Pathologically, the hydrops did not extend into the vestibular part of the labyrinth.

The epithelial part of the vestibular apparatus and first neurone of the vestibular paths revealed surprisingly slight pathological changes while the vestibular nuclei studied (lateral, medial and superior) showed enormous loss of ganglion cells and very severe degenerative changes in the remaining ganglion cells. The changes in the vestibular nuclei of the brain stem were deemed to be the severest observed in the nuclei of the cranial nerves.

On the basis of the pathological findings it is reasonable to attribute the vestibular symptoms to the brain.

Other Neurological Manifestations

It should be noted that the patient had other neurological manifestations (1) positive Romberg's sign (2) deviation to the left during walking and (3) paresis of the right vocal cord. These symptoms could be either of peripheral or central origin while the cataleptic attacks must be of central origin.

CONCLUSIONS

The diffuse degeneration of the brain demonstrated both macroscopically and by histological studies may offer an adequate explanation both of the symptoms of central origin and the hearing loss especially for high frequencies, as well as of the symptoms from the vestibular apparatus and to some extent the hearing loss for low frequencies.

In our opinion the clinical and neuropathological changes in the patient and

the results of our studies of the literature suggest that the aetiology of Meniere s disease should be sought not only in the labyrinth as a consequence of endolymphatic hydrops but also in the pathological changes in the brain

SUMMARY

The brain and temporal bones of a patient with Menière s disease were subjected to histological studies

The patient revealed the greatest hearing loss in the left ear The bilateral hydrops was most pronounced in the right ear while the changes in the spiral ganglion and the peripheral part of the acoustic nerves were severest on the left side The changes in the cerebrum brain stem and the glial part of the acoustic nerves were of much greater severity than those observed in the peripheral neural elements *Accordingly, we believe that the hearing loss was mainly of central origin*

The caloric response was markedly reduced on both sides and the patient suffered from attacks of vertigo and had a feeling of unsteadiness during gait The histological changes in the peripheral part of the vestibular apparatus and the vestibular ganglion were surprisingly slight while severe degeneration of the central vestibular nuclei was observed

In addition, the patient presented symptoms of central origin (cataleptic attacks) along with symptoms which may in part be due to cerebral damage (positive Romberg s sign deviation to the left during walking and paresis of the right vocal cord)

In our opinion the clinical and histological changes in the patient and the results of our studies of the literature suggest that the aetiology of Meniere s disease should be sought not only in the endolympathic hydrops but also in the pathological changes in the brain

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ULTRASONIC IRRADIATION OF THE LABYRINTH

SOME EXPERIMENTAL AND CLINICAL OBSERVATIONS

By

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Abstract

Animal experiments seem to have given plausible explanations for the favorable clinical results obtained in Meniere s case Ultrasound reduces the function of both the neuro epithelium and the secretory epithelium in the labyrinth The effect of ultrasound on the bony walls of the labyrinth has been studied by means of labelling with te racycline

The effect of ultrasound on the inner ear has been studied at the Department of Otolaryngology in Uppsala since 1959 Our research has comprised partly of animal experiments and partly of clinical treatment of some 60 cases of Meniere's disease (Sjoberg, Stahle, Johnson and Sahl, Acta Oto Laryng 1963, Suppl 178)

The effects of ultrasound are thermal, chemical and mechanical and result in a more or less widespread tissue damage, depending upon the dose and frequency Nerve tissue has been found to be more sensitive to ultrasound as compared to skin, muscle, bone and capillaries Definite as well as reversible lesions have been described In experiments on animals, the Uppsala group has shown that ultra sound can bring about a reduction in labyrinth function or in other words, a reduced vestibular excitability These reductions in function are complimented by certain characteristic morphological changes The animals used in these experiments have been pigeons, mainly for these reasons, 1) the inner ear is easily accessable, 2) the labyrinth function can be tested by means of nystagmography

METHODS

The new Uppsala apparatus, *Ultrapoint*, operating at a frequency of approximately 1 25 mc has been used to apply the ultrasound The tip diameter of the transducer (the diameter of the working area of the treatment head) has been 1 5—2 6 mm The tips are interchangeable, the smaller ones having been used in animal irradiation The power used in animal experiments as well as in the treatment of patients with Menière's disease has been from 1—3 watts

The pigeons' labyrinth have been tested *electro nystagmographically* according to a method given by Aschan, Bergstedt and Stahle, 1955 This involves in principle, a registering of the pigeon's head nystagmus with the help of a photo cell and a recording instrument (Mingograph)

A *rotatory test* (AD test) *described* in 1957 by Stahle, has been used as stimulus

for the pigeons This test includes an acceleration of $6^{\circ}/sec^2$ for 10 seconds, followed by rotation at constant speed for about 1 minute, which is broken off by a retardation to stop with, likewise, $6^{\circ}/sec^2$ This test is done first clockwise and then counter clockwise

SOME RESULTS

A non irradiated pigeon having been given the AD test with all four stimuli, will demonstrate a nystagmus of 20—25 seconds after each stimulus An example of the normal result is seen in the four topmost curves in Fig 1 (Pigeon No 15) The first of these curves shows a right beating nystagmus caused by the

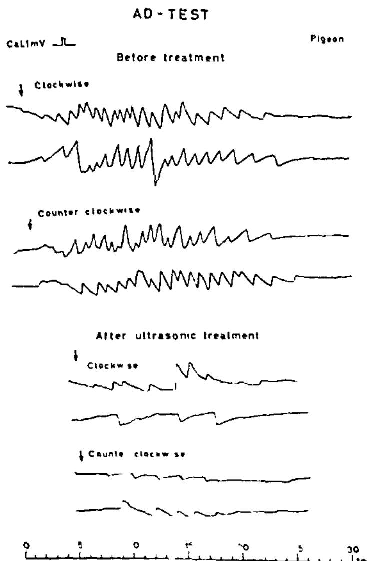


Fig 1 Rotatory tests on Pigeon No 15 Before bilateral ultrasonic irradiation normal reactions (the four topmost tracings) Three weeks after irradiation greatly impaired function (the four lower tracings)

acceleration to the right, the next curve shows a left beating nystagmus caused by the following retardation, etc

This animal (Pigeon No 15) was irradiated with 1 watt for 45 seconds towards each of the three semicircular canal's ampullae — first on the left, then two weeks later, on the right side The rotatory test three weeks after the last irradiation shows greatly impaired function (the four lower tracings in Fig 1) The animal was sacrificed three weeks after the last irradiation Histological examination revealed minor changes in the labyrinth The sensory and secretory epithelium in the ampullae were partly degenerated with vacuolation and pyknosis of the nuclei The cupulae were collapsed and shrunken The walls of the semicircular canals were thickened here and there and showed a tendency to proliferation of fibroblastic tissue in the perilymphatic space

Larger doses of ultrasound can completely eliminate the pigeon's labyrinth function An example of this is Pigeon No 4 as illustrated in Fig 2 Irradiation was carried out bilaterally with a two week interval and at a power of 1 watt for 4 minutes, the beam being directed towards the ampulla of the lateral semicircular canal and the vestibule Before irradiation, normal reactions were registered in the rotatory test Five weeks after irradiation, no nystagmus could be elicited (the four tracings to the right in Fig 2)

The histological changes in this animal were considerably advanced There was a serious degeneration in the sensory as well as the secretory epithelium in the inner ear, elimination of the cupulae and other otolith-membranes, dege-

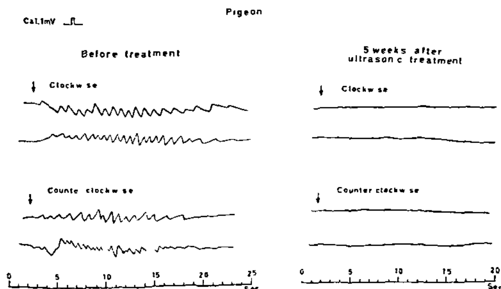


Fig 2 Rotatory tests on Pigeon No 4 *Before bilateral ultrasonic irradiation normal reactions* Five weeks after irradiation no reactions can be elicited The arrows indicate the start of acceleration and deceleration

neration of the nerve fibres, vascular changes with thrombosis and extensive lesions of a callus type in the bony walls The perilymphatic space was partly filled up with new tissue due to a strong fibroblastic activity.

The results of ultrasonic irradiation on pigeons is summarized as follows —

Histological

1 Degeneration of neuro-epithelium and secretory epithelium in the ampullae, utricule and saccule

2 Collapse or decomposition of the cupula

3 Obliteration to varying degrees of the perilymphatic space due to strong fibroblastic activity

4 Lesions on the bony labyrinth wall, callus like formations

5 Thickening of the membranous labyrinth wall

6 Degeneration to varying degrees of neuro epithelium and secretory epithelium in the lagena

Functional

7 During irradiation — "irritative" → "paralytic" nystagmus

8 After irradiation → impaired vestibular function, verified by rotatory test and electro-nystagmography

I should like to enlarge on a few of the above mentioned points, namely, 1, 3 and 4, which I consider to be most contributory to the good clinical results —

ad 1 Degeneration of the sensory as well as the secretory epithelium should lead to *reduced vestibular function as well as a decrease in endolymph secretion*

ad 3—4 The obliteration of the perilymphatic space as well as the proliferative changes in the bony walls, which are of callus type, can be presumed to affect to a significant degree the labyrinth's hydrodynamic status This could possibly add to an elimination of function

TETRACYCLINE LABELLING OF THE ULTRASONIC BEAM[1]

The extent and depth of the ultrasound's destructive effect has been studied by the use of *tetracycline* This substance has a special affinity for bone tissue and marks all sites of new bone formation (Milch and co-workers 1957, 1958, 1961, Hulth & Olerud, 1962) Given by mouth or parenterally, tetracycline produces a yellowish fluorescence from newly formed bone in ultra violet light

Three weeks after unilateral irradiation, several pigeons were given a 25 mg dose daily for 48 hours before sacrificing

After fixation and dehydration, the skulls were transferred to unpolymerized methyl methacrylate for 24 hours and then embedded in polymerized methyl methacrylate with 5 per cent butylphthalate added After complete polymerization, which took 3—4 days, thin slices of bone were sawn and sanded down to a thickness of about 200 micra

[1] To A. Hulth M.D and S Olerud M.D we give our warmest thanks for their help in this part of the work.

Fluorescence microscopy revealed a strong luminous fluorescence from the irregular bony walls of the irradiated labyrinth indicating a lively new growth of bone The changes were most pronounced in the contacting surface, but a fluorescence was suggested even within the lamina interna close to the brain, which latter showed no fluorescence in the beam s path

The experiment with tetracycline labelling shows that ultrasound can develop bone injury, and that the bone reacts and heals with callus like formations

NYSTAGMUS DURING ULTRASONIC IRRADIATION IN MAN

During ultrasonic irradiation nystagmus is produced with the application of adequate dosage and technique This nystagmus follows a definite pattern and has been studied by means of electro nystagmography Three main phases in the nystagmus pattern can be identified — the *irritative intermediary and paralytic* The irritative phase which comes first and is then dominant, is characterized by a homolateral "irritative' nystagmus of high intensity This is followed in some cases by an intermediary phase lasting 1—10 minutes during which no nystagmus can be elicited by the ultrasound The paralytic phase comes last and is marked by a contralateral nystagmus (that is to say, beating in the direction away from the irradiated ear) of low intensity and with a duration of from a few hours up to some weeks

The appearance of a paralytic phase, characterized by a contralateral nystagmus, has earlier been generally accepted as a sign of permanent labyrinth destruction (Arslan 1953, 1958, 1962, Angell James and co-workers 1960) This is not wholly correct. *To the contrary, extensive investigations of irradiated patients by means of the caloric test have shown that the labyrinth function — expressed as caloric excitability — is eliminated only in exceptional cases, though reduced in the majority of cases, but in not a few cases has remained unchanged*

The direction of nystagmus on the operating table should not be taken as a definite criterion of the labyrinth's function in the future The contralateral nystagmus can actually be provoked time after time during ultrasonic irradiation interchangeably with the homolateral "irritative" nystagmus — a fact which shows that the labyrinth still functions well Not until a clear, persistant contralateral nystagmus first comes up during the irradiation can breaking off of the treatment be considered

The contralateral nystagmus which appears repeatedly during irradiation has been named *pseudo-paralytic*, and it has been registered in the majority of our, up to now, 65 cases treated The reversal of nystagmus from homolateral ("irritative") to contralateral always takes place during the short pause in the irradiation which is usually made every 4—5 minutes in order to check the apparatus and change hands The phenomenon is illustrated in Fig 3 — a pseudo-paralytic nystagmus is recorded in tracings Nos 4 and 6, whereas the nystagmus in tracings Nos 8—10 have been judged as true paralytic.

The explanation for the appearance of a pseudo-paralytic nystagmus could

neration of the nerve fibres, vascular changes with thrombosis and extensive lesions of a callus type in the bony walls The perilymphatic space was partly filled up with new tissue due to a strong fibroblastic activity

The results of ultrasonic irradiation on pigeons is summarized as follows —

Histological

1 Degeneration of neuro epithelium and secretory epithelium in the ampullae utricule and saccule

2 Collapse or decomposition of the cupula

3 Obliteration to varying degrees of the perilymphatic space due to strong fibroblastic activity

4 Lesions on the bony labyrinth wall, callus like formations

5 Thickening of the membranous labyrinth wall

6 Degeneration to varying degrees of neuro epithelium and secretory epith elium in the lagena

Functional

7 During irradiation — 'irritative' → 'paralytic nystagmus

8 After irradiation — impaired vestibular function, verified by rotatory test and electro nystagmography

I should like to enlarge on a few of the above mentioned points, namely, 1, 3 and 4, which I consider to be most contributory to the good clinical results —

ad 1 Degeneration of the sensory as well as the secretory epithelium should lead to *reduced vestibular function as well as a decrease in endolymph secretion*

ad 3—4 The obliteration of the perilymphatic space as well as the proliferative changes in the bony walls which are of callus type, can be presumed to affect to a significant degree the labyrinth s hydrodynamic status This could possibly add to an elimination of function

TETRACYCLINE LABELLING OF THE ULTRASONIC BEAM[1]

The extent and depth of the ultrasound s destructive effect has been studied by the use of *tetracycline* This substance has a special affinity for bone tissue and marks all sites of new bone formation (Milch and co workers, 1957, 1958, 1961 Hulth & Olerud, 1962) Given by mouth or parenterally, tetracycline produces a yellowish fluorescence from newly formed bone in ultra violet light

Three weeks after unilateral irradiation, several pigeons were given a 25 mg dose daily for 48 hours before sacrificing

After fixation and dehydration, the skulls were transferred to unpolymerized methyl methacrylate for 24 hours and then embedded in polymerized methyl methacrylate with 5 per cent butylphthalate added After complete polymeriza tion, which took 3—4 days thin slices of bone were sawn and sanded down to a thickness of about 200 micra

[1] To A Hulth M D and S Olerud M D we give our warmest thanks for their help in this part of the work

caloric nystagmus countering the first strong reaction, and finally the reversal of paroxysmal positional nystagmus described by Stahle 1960

Ultrasonic treatment of the labyrinth is still far from complete It is now, though, clearly shown that by means of a directed ultrasonic beam it is possible to reduce the labyrinthine function in man with preservation of the hearing A series of animal experiments, similarly have given information about those changes which we can except to come about also in the human ear There has been opened hereby, a whole new aspect of labyrinthine surgery, which *allows us to selectively destroy structures inside the inner ear without opening the bony walls*

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INTRAVENOUS XYLOCAINE IN THE TREATMENT OF ATTACKS OF MENIÈRE'S DISEASE

By

T Gejrot

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The use of xylocaine in the treatment of attacks of Menière's disease is based on the similarity between these attacks and epileptic vertigo In both cases there may be aurae, cold sweat, rotatory vertigo nausea, vomiting and increased salivation, and they are distinguishable only by the degree of these manifestations and the hearing loss in Menière's disease Among 120 patients that were considered to have symptoms of vestibular disturbances in their epilepsy Smith (1960) found about 60 with pure rotatory vertigo As many had visceral and autonomic disturbances in the form of vomiting, nausea, increased salivation, etc Twenty had tinnitus

In 1954 Bernhard & Bohm demonstrated that local anaesthetics, administered intravenously, had an excellent effect in attacks of epilepsy Of a number of local anaesthetics examined, xylocaine was found to have the best relation between anticonvulsive effect and toxicity In clinical experiments the authors found that they could interrupt attacks of grand mal or Jackson's epilepsy with a single dose of 1—3 mg per kg of body weight, the effect was evident after 35—40 seconds, and it lasted as a rule for 15—20 minutes, depending to some extent on the dose

Similar symptoms in attacks of Menière's disease and epilepsy have prompted the use of xylocaine in antiepileptic dose in attacks of Menière's disease A one per cent solution without epinephrine is used at the dose of 1 mg per kg of body weight, administered at the rate of 6 mg per minute It is given only during attacks and in periods of severe nausea Eleven patients have been receiving this therapy on a number of occasions

CASE REPORTS

Case 1 — A 29-year old woman arrived at the hospital with rotatoric vertigo, severe nausea and tinnitus in her left ear She could not turn her head without vomiting, and displayed hysterical emociety Two minutes after injection of 6 ml of xylocaine (her body weight 60 kg) the attack was interrupted and the patient was able to get up from the bed She had no tinnitus for about 20 minutes Her feeling of vertigo was diminished and the nausea banished She was able to return to work

Case 2 — A 55 year old man with right sided Menière's disease had been treated conservatively for the last 10 years He now had slight episodes of in

creased tinnitus, slight rotatory vertigo and rather severe nausea Two or three minutes after an injection of xylocaine the nausea was usually interrupted for several hours, after which it returned in a diminished form He had no tinnitus for about 20 minutes The feeling of rotary vertigo persisted but it was not so severe as to bother him, and he was able to return home

The results of this antiepileptic therapy in attacks of Meniere s disease has been strikingly good, especially as regards the vegetative reactions In most cases the nausea and vomiting disappeared dramatically after a minute or so, and the patients could move about freely In some of the cases the relief was not complete, but still enough for the patient to sit up and take a meal without complications Where the symptoms are continous xylocaine infusion may be instilled In 2 cases there was on several occasions complete recovery from the severe attacks, and the patients were able to return to work In this antiepileptic dose xylocaine has no sedative side effects (Bohm 1959) Some patients are at present receiving necessary injections of xylocaine from the works medical officer, and they need not return to the hospital

In all cases tinnitus disappeared for about 20 minutes after which it gradually returned Occasional improvements in the hearing were recorded on pure tone audiograms but as a rule no differences were noted In 5 cases nystagmus was recorded Xylocaine had no effect on the appearance of nystagmus (Fig 1)

In order to illustrate the effect of xylocaine it has been studied in other states than Menière's disease where vestibulovegative disturbances are frequent, such as caloric tests and provoked sea sickness Fig 2 shows the results of an attempt to record a nystagmogram on a patient with a tendency for sea sickness On caloric irrigation the patient experienced dizziness, nausea and anxiety and the test had to be discontinued After an injection of xylocaine at the antiepileptic dose the test could be resumed with no discomfort At the dose of 1—2 mg per kg of body weight xylocaine has no influence on induced vestibular nystagmus (Gejrot 1963) In provoked sea-sickness the effect of xylocaine was studied by recording the skin resistance According to Sjoberg (1931) two forms of sea sickness can be distinguished — the asthenic type with depression, increased salivation and diarrhoea, and the agitatoric type with vomiting, nausea and anxiety Xylocaine at the antiepileptic dose proved to have a favourable and recordable effect, especially on the agitatoric type (Fig 3) Blind tests with saline had no effect

The mode of action of xylocaine is still not quite clear Wieding (1959), among others, has shown that, like novocaine, xylocaine has an anticholinergic action For that reason Duchon et al (1959) used novocaine intravenously in the treatment of Meniere's disease By means of careful intravenous injections of 5 ml of 2 per cent solution for 20 days, Duchon et al banished the symptoms in 6 cases for 4—8 months there were improvement in hearing and vestibular function, and reduction of tinnitus Their use of novocaine was based on Williams (1953) opinion that Menière's disease is due to a cholinergic hyperactivity

That xylocaine has a central action is known from studies of its effect on ex-

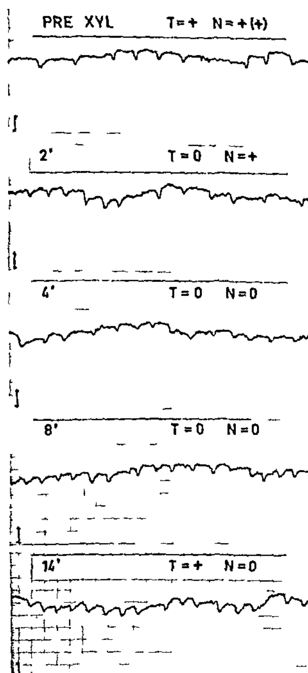


Fig 1 The effect of xylocaine on nystagmus t nnitus (T) and nausea (N) in a cas of Meniere s disease

PRE XYL V = +++ N = ++

POST XYL V = (+) N = 0

Fig 2 The effect of xylocaine on the vestibulovegetative functions on caloric irrigation. Before the injection *the test had to be discontinued owing to nausea* (N) *and* vertigo (V). After the injection a record could be made without discomfort

perimental epilepsy and other types of central activity (Bernhard & Bohm 1955) Analogously, in Menière's disease xylocaine should exert its effect on the vestibular cortex and its links with vegetative centres The encephalogram pattern in Menière's disease, studied by Petersén (1962), sometimes showed changes It has never been studied during attacks Some authors consider that Menière's disease may have a central onset mechanism, primary or secondary (Grove 1941, Nager 1949)

The favourable effect of antiepilepsy therapy on the similar vegetative disturbances in agitatory attacks of Menière's disease, sea sickness and caloric stimulation suggests an epileptic equivalent

	1	2	3	
SR	++	-	++	*Ag*
BE	++	++	++	As
ASC	++	-	++	*Ag*
GF	++	(+)	+(+)	*Ag*
CR	+(+)	(+)		As
LE	++	(+)		As
SH	++	++		As
OE	++	-		*Ag*
NG	++	-		*Ag*

Tab I The effect of xylocaine on provoked sea sickness Tests 1 and 3 without xylocaine, test 2 with xylocaine Six of the subjects did not dare to repeat the provocation The effect was more favourable in the agitatoric type (Ag) of provoked sea sickness than in the astenic type (As)

SUMMARY

The effect of xylocaine on epileptic attacks suggested a study of its effect in attacks of Menière's disease, as the symptoms can be very much alike in the two conditions The results were found to be excellent, especially as regards the vegetative dysfunctions In attacks of Menière's disease the tinnitus disappeared for 20 minutes, vomiting generally disappeared for good and nausea for an hour or two Nystagmus was unaffected A comparison was made with the treatment for sea sickness In epileptic attacks xylocaine acts at the cortical level In Menière's disease it possibly acts on the vestibular cortex

ZUSAMMENFASSUNG

Die Wirkung von intravenosen Dosen von Xylocain auf epileptische Attacke veranlasste ein Studium der Wirkung in der Menièrischen Krankheit, da die Symptome sehr ähnlich sein konnen Die Ergebnisse waren sehr gut, speziell betreffs der vegetativen Storungen In den Attacken der Menièrischen Krankheit horte das Sausen wahrend 20 Minuten auf Erbrechen verschwand im allgemeinen uberhaupt und die Übelkeit wahrend einer Stunde oder zwei Nystagmus wurde nicht beeinflusst Ein Vergleich mit der Behandlung der See Krankheit wurde gemacht In epileptischen Attacken ist Xylocain zentral im Grosshirn wirksam In Fallen von Menièrischer Krankheit scheint Wirkung von Xylocain in der vestibularen cortex moglich zu sein

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MECHANICAL COMPONENT TO DEAFNESS IN MENIÈRE'S DISEASE

By

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Abstract

Deafness in Menière's disease is of a perceptive type but not infrequently a mechanical component is found Such a case is described in which the intra auricular muscle reflexes have indicated that a normal transmission system in the middle ear existed It is presumed that the mechanical component to the deafness is dependent on charged hydrodynamic conditions in the inner ear

The active phase of Menière's disease is audiologically characterized by some degree of deafness, usually in the lower frequencies This deafness is mainly of the perceptive type, with recruitment, pitch displacement (diplacusis binauralis) and reduced tolerance of high sound intensities These symptoms together form a definite criterion of cochlea disease

In the very early stage, before the attacks of dizziness have begun, one can often find a mechanical component in the lower frequency hearing loss Since this particular phenomenon has been but little heeded in medical litterature, one feels justified in mentioning the following case

The patient was a 41 year old woman who complained of attacks of dizziness, deafness and buzzing in the right ear The otologist who sent her to us found on doing Weber's pitch-fork test with 256 cps that lateralizing was to the right and Rinne's test was ±

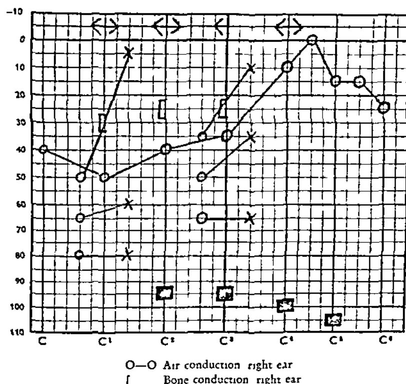
On examination we found normal ear drums Pure tone audiogram showed a gap between air and bone conduction of 10—20 db in the frequency area 250—1000 cps Fowler's balance test showed recruitment and the speech audiometry curve was of the typical cochlear type

On account of the history of the illness and the audiometry findings the diagnosis of Meniere's disease is considered certain

In addition to the perceptive hearing loss there was also found a conduction loss, when tested with adequate masking ad modum Hood

The hearing on the left ear was normal In Weber's audiometric test the patient showed lateralizing to the affected right ear with the 1000 cps tone, otherwise no lateralizing Distinctly registerable tympanic reflexes indicated a normal transmission apparatus in the middle ear Nothing pathological was found on electro nystagmography and caloric vestibularis tests

Bocca and Perani suggested the possibility of vestibular hearing by saccular receptors in some cases of perceptive deafness In such cases the bone conduction curve will be better than the condition of the cochlea might indicate This could



O—O Air conduction right ear
[Bone conduction right ear

possibly also be the case in Meniere's disease at a stage so early that only cochlear and not *vestibular symptoms have displayed*

On the other hand the perilymph belongs to the conduction system In Menière's disease an increased intralabyrinth pressure with hydropsis could represent a mechanical hindrance to the passage of sound waves which, in audiometry, is seen as a fall in the air conduction curve — as an addition to bone conduction loss

Further research must decide what mechanism lies behind the mechanical deafness in Meniere's disease In practical otology it is important that one is aware of the symptom

EXPERIMENTS IN ENDOLYMPH CIRCULATION

By

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Many years of effort in the treatment of Menière's disease have been inhibited by lack of basic knowledge Although multiple theories about the cause of this affection have been proposed, most scientists at present seem to agree that at least part of the symptoms depend on an imballance in the system regulating the circulation of the labyrinthine fluids Information about this system is, however, limited It seems reasonable to assume that active research on problems concerned with the mechanism of secretion and absorbtion of the endolymph will throw light on the etiology of Meniere's disease

Stacy Guild (1927) presented a theory on the circulation of endolymph based on studies of the endolymphatic sac He showed that the endolympathic sac proper (Fig 1) is a structure of highly significant architecture with a specialized epithelium and which also contained a large number of what seemed to be macrophages

Guild suggested that the endolymph is secreted by the stria vascularis, flows through the ductus reuniens to the saccule and through the endolyhphatic duct out to the endolymphatic sac where it is absorbed This theory has ben supported by H C Andersen (1948), Guild (1927) and others who injected staining solutions in the fluids of the inner ear, thereby showing that a significant amount of stain was taken up by the macrophages in the endolymphatic space

Recently several authors have suggested a passage of fluids and ions through the Reissner's membrane Althman and Waltner (1947), Gisselson (1949) and Rausch et al (1960, 1963) The possibility for secretion of endolymph from a separate system within the vestibular part of the labyrinth has been suggested by Dohlman et al (1960), Wersall and Hawkins (1961) and Kimura Lundquist and Wersall (1963) and others

The aim of the present paper was to study the passage of particles injected into the cochlear duct, within the endolymphatic spaces

MATERIAL AND METHODS

Young adult guinea pigs with normal Preyer reflex were used Appr 0 1 cc of a colloidal solution of 0 25 % Silver was injected in the scale media of the basal turn of the cochlea The surgical approach was from the anterior side A small hole was also drilled in the scala media of the third turn, to check the outflow of silver solution while injecting in the basal turn The holes were closed with wax



Fig 1 Light microscopic view of the endolymphatic duct and sac The duct and the prox mal portion of the sac gradually widen into the first part of intermediate portion of the sac which is completely covered by bone (lower left hand corner) followed by the se ond active part outside bone close to the paraflocculus and the transverse sinus (upper right hand corner) In *the extreme end, the sac flattens into the distal portion Heidenhahn Susa* × 35



Fig 2 Light and dark cells from a crypt in the intermediate portion of the endolymphatic sac the dark cells with more dense cytoplasm and a less number of m crovilli Osm um tetroxide × 2 600

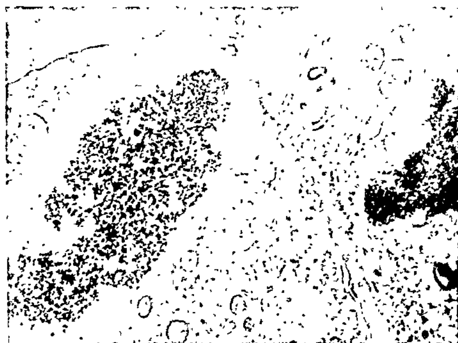


Fig. 6. Part of intermediate portion of the endolymphatic sac of a guinea pig injected with colloidal silver solution into the scala media of the basal turn, showing big inclusion bodies containing numerous silver granules. Osmium tetroxide × 20 000

and the animals were sacrificed after 24 hours After decapitation the brain and cranial nerves were carefully dissected out from the skull without disturbing the endolymphatic sac and its adherence to the transverse sinus

The specimen was then fixated in Osmium tetroxide imbedded in Epon, and photographed with a Siemens Elmiscope I Electrone microscope

RESULTS

Silver granules (Fig 4) were found in a significant amount only in the endo lymphatic sac The particles were engulfed by the macrophages in the lumen of the sac and a very large number of silver granules were found in their cytoplasm (Fig 5 a) In the intermediate portion of the endolympatic sac the macrophages were seen very close to the surface of the epithelial cells The surface of these cylindrical cells showed a high degree of activity Finger like protrusions from the surface invaginated the plasma membrane of the macrophages and several protrusions enclosed part of the macrophages in what seemed to be an active macro phage activity (Fig 5 a, b) In other cells of the epithelial covering of the endo lymphatic sac, large parts of already engulfed macrophages with silver inclusions were found in the cytoplasm (Fig 6)

The organ of corti, in the area where silver was injected degenerated appar ently because of the toxicity of the silver solution No significant amount of silver was found in the stria vascularis or other parts of the epithelia covering the cochlear duct and the rest of the labyrinth

DISCUSSION

In a recent publication Lundquist Kimura and Wersall described the fine structure of the epithelial lining of the endolymphatic sac and duct The cells in the intermediate portion of the sac were found to differ from the rest of the cells They appeared to be more specialized, their surface membrane contained a large number of finger like protrusions, and there were frequent vessicles close to the surface These findings suggest an active pinocytotic activity in the cells (Fig 2, 3)

The bottom part of the cells showed marked infolding of the plasma mem brane, similar to that found in other cells with secretory or absorbtive function (Maxwell and Pease 1956) It was thus suggested that these cells had a capacity to absorb fluid from the endolymphatic space and pass that fluid on to the capillaries

The capillaries were found to contain pores in the endothelial cell wall similar to the pores described in the kidney capillaries (Rhodin 1962)

The present investigation supports the idea first proposed by Guild and later by several other investigators that part of the endolymph passes from the coch lea to the endolymphatic sac In earlier studies most injected solutions have been taken up by the macrophages in the endolymphatic sac, but it has been very difficult to follow the injected particles out through the epithelium

The present investigation clearly demonstrated, however, that the cells of the epithelial wall of the endolympatic sac have a considerable capacity to act as macrophages Small as well as large particles and fluid vessicles pass through the cells and although we have not been able to follow the particles to the capillaries yet, it seems highly possible that a good deal of the endolymph and small particles, absorbed by cells of the intermediate part of the endolymphatic sac, is passed on to the capillaries in the connective tissue wall of the sac

SUMMARY

The passage and distribution of material injected into the cochlear endolymph in guinea pigs is described with special regards to the circulation of endolymph Silver granules injected in scala media of the basal turn of the cochlea were found in a significant amount only in the endolymphatic sac, where the cells of the epithelial wall have a considerable capacity to act as macrophages Silver granules and fluid vessicles were seen incorporated in the cytoplasm of the epithelial cells in the intermediate portion of the sac

ACKNOWLEDGEMENT

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DISCUSSION

H Myrhaug

It is a common observation that deafness, tinnitus and headache are symptoms that frequently follow vestibular vertigo, f ex Menière's disease (6) Therefore it would not be without foundation to suppose that all these ailments had a common cause

By observation of this phenomenon it is found that the impaired hearing may fluctuate a great deal, as is also seen in Menière's disease The fluctuation of the deafness seems to be of functional origin connected to the soundconducting apparatus This point will be considered later

First it must be mentioned that the middle ear structures are closely related to the jaws and the masticatory muscles Thus the tensor tympani and the tensor veli palatini muscles have innervation in common with the masticators (n trigeminus) Muscles corresponding to the tensor muscles are found in lower vertebrates to be connected to the masticating apparatus The middle ear ossicles, malleus and incus, are also considered to originate from jaw bones

Those observations ought to give some association as to the connection between jaw function and the soundconducting system of the middle ear But considerations of this kind are rarely met with in literature on otology Most authors seem to be interested solely in the labyrinthine capsule and its contents *Fowler jr* makes an exception when he states that bite abnormalities is a known cause of tinnitus (1) One may, however, wonder if this is a common knowledge among otologists Because this is an important point Could the cause of tinnitus be made clear, much had been won Tinnitus and vertigo are parallel symtoms, and symptoms only Because neither tinnitus nor vertigo are actually diseases They are considered as being conveyor symptoms in a pathological functional process, and the author will here try to entangle the threads that seem to lead to the basic fault — Then one has to start with the masticating apparatus

In the period 1952—1962 the author has examined 1541 jaw cases, i e patients with bite anomalies Most of them had symptoms of temporo mandibular joint arthrosis, and the majority (well 70 %) also suffered from headache, frequently unilateral, as well as neuralgic type pains of the face, neck, shoulder and arm localized to the same side as the head pains and the arthrotic symptoms All patients hade one or more of those symptoms simultaneously

Of these *1541 cases*

437 had noticed disturbances of equilibrium, infrequently crippling,

500 had acoustic symptoms such as tinnitus, popping sensations in the ear and otherwise hypacusis partly of fluctuating character,

324 had otalgia, usually on same side as the temporo mandibular arthrosis and bite anomaly

It is to say that every 3 patient with peripherial symptoms from bite anomalies had acoustic symptoms and every 3 5 patients had disturbances of balance

As to the headache caused by a faulty bite, details can not be dealt with in this connection It must suffice to state that abnormal bite conditions are the most frequent mechanism of headache This is recognized by neurologists but few are taking the consequences of it

Bite anomalies are of various kind But let us consider one type that is easily recognized, that one which is brought about by the loss of molars (Fig 1) When this anomaly is bilateral, it leads to a typical loss of vertical dimension of the jaws, termed closed bite (Fig 1) This gives as a result reduction of the distance between the two ends of the masticators concerned with closing of the jaws, which again leads to a paradoxic contraction of these muscles These closers will have to contract beyond their normal physiological ability, and if the bite is not corrected, this will be a permanent state of affairs and the muscles will suffer a stress that may last for the lifetime

The physical irritant from such a bite anomaly will also affect the tensor muscles while they are supplied by the same nerve The synergy of the tensor muscles and the masticators not commonly recognized, can easily be demonstrated by visual observation as well as by electromyographic registration by deflection of the tympanic membrane (for instance during operation for otosclerosis, when one has access to the middle ear) Subsequently there seems to be a state

of concentration of the tensor muscle of the middle ear, synergetic with the masticators As a consequence of this there is in the first place certain changes of the tympanic *membrane (4)*. Details must here be omitted But a long-standing contraction of the tensor muscle *will also* affect the other structures in the middle ear Most important in this connection is the stapedial muscle with which there is a well balanced cooperation When the tensor tympani muscle is contracting, the stapedial muscle will answer with same manouvre The *result of this is a* stiffening of the soundconducting apparatus, why the impedance increases *Here is the key* to understanding as well as to the origin of popping sensation in the ear and fluctuation of *hearing*

Secondly a muscle under stress of long standing (contraction) will suffer exhaustion The masticators which are in the same category as the tensor muscles, but are in the *posession of* muscular antagonists, seem to be more resistant to stress than the small endaural muscles where

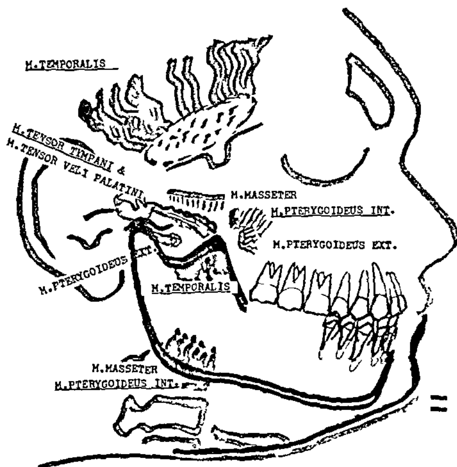
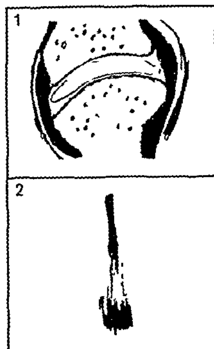


Fig 1

Bite anomaly — In casu Loss of molar support

Sequela — Abnormal elevation of the mandible (closed bite) Forshortening of masticatory muscles (the closers) Paradoxic contraction of same Synergetic contracture & eventually clonus (myorhythmia) of tensor muscles (Nb' elastic fibres) Vibration (autogenous) of the soundconducting system Rocking stapes & fluid motion in the lymphatic system Stimulation of sensory organs of inner ear Impression of sound (tinnitus) Disturbed equilibrium (vertigo) Intermittant intralabyrinthine fluid pressure (swell) Hydrops", destruction of sensory epithelium.



1) Section of the incudostapedial joint The elastic fibres of the capsule appear black.

Fig 2

2) Longitudinal section of stapedius muscle and tendon The elastic fibres appear black (After Harty.)

such antagonists are lacking. The endaural muscles are instead *supplied* with tendons which are composed of elastic tissue fibres, as are also the joint capsules of the ossicular chain and the foot plate ligament (Fig 2) The soundconducting apparatus thus seems to have a rather elastic and labile suspension, and any displacement must be corrected by elastic recoil (2) Therefore a distortion of the soundconducting system is apt to give uncontroled movements of the stapedial footplate This seems to be the case during long standing contraction states and exhaustion of the middle ear muscles which give rise to clonus or myorhythmia of these muscles. — The autogenous vibration produced by this action will also affect the lymph system of the inner ear (Fig 3) In the first place the effect is an impression of sound percepted as tinnitus In rare instances *the palatal tensor muscle is also taking part, the effect of which is an objective tinnitus* (Compare film 'Clicking ear and pharyngeal tic associated with functional disturbances of the jaw," later in the program of the procedings)

In the second place the sense cells of the organ of equilibrium are affected When the *stapedial footplate is rocking violently, not only an impression of sound is perceived, but also* a paroxysm of vertigo is experienced — The syndrom of Lermoyez for instance, demonstrates clearly how impaired hearing, — due to cramping contraction of endaural muscles, — is succeeded by clonus (myorhythmia) which gives as a result vertigo and tinnitus and an impression of improved hearing — C est la vertige qui fait entendre!

The combination of headache, tinnitus and vertigo is thus easily explained, and the psychological aspects which entails, are also well understood It may all be due to muscular dysfunction on the basis of physical irritants from a faulty bite A simple explanation it seems (The possibility of otosclerosis being explained by the same mechanism is another story)

From this point of view there should be no reason to distinguish between Menière s disease and other forms of vestibular vertigo such as pseudo-Menière etc The difference is a matter of *degree only, and the more severe form happens to be connected to the name of Menière*

The fluid motion of the lymph which gives rise to these sense reactions, also exercises an intermittant pressure on the labyrinthine walls, like waves braking on the shore (5) The effect of waves in a closed system may be quite enormous, and the pathological changes in the labyrinth of which 'hydrops is a part, may well be explained as an action of such intermittant pressure *from* an abnormal fluid motion of the lymph

Summary

Disturbances of balance occured in one in 3 5 and acoustic symptoms were found in one in 3 out of 1541 patients who had been examined during a period of 10 years for *malocclusion*, when the dysfunction had led to clinical symptoms such as temporo mandibular joint arthrosis, headache and neuralgia about the head and neck and shoulders

The labyrinthine symptoms are interpreted as functional disturbances in the soundconducting (locomotor) system of the middle ear caused by dysfunction of the masticating apparatus, the muscles of which are in synergy with the tensor tympani and tensor veli palatini muscle

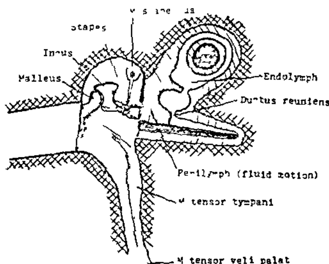


Fig 3

The organ of hearing and balance

Fluid motion in the lymph is indicated the result of autogenous vibrations of the sound conducting apparatus in the middle ear — The cochlear as well as the vestibular structures of the inner ear is found to be influenced by this mechanism

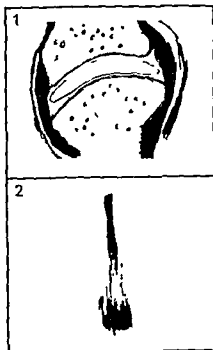
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Ebert

J ai publ é en 1952 dans les « Annales d Oto Laryngologie » un article intitulé « Traitement de la rhinite chronique simple de la sinusite maxillaire et ethmoidale chronique simple et de l epirhinite chronique »

Depuis 1930, j avais traité dans ma pratique privée 571 patients se plaignant essentiellement des troubles suivants de coryzas répetes de plus ou moins longue durée ou seulement de coryzas prolongés, et généralement le patient se plaignait plus ou moins d avoir le nez bouché En pratiquant la ponction du sinus maxillaire conformément à la technique recommandee par le professeur Leegaard senior au VIème congrès nordique d otologie à Stockholm en 1937, avec une canule de ponction rectiligne selon Lichtwitz je n ai obtenu dans ces cas en général qu un liquide legerement trouble Au bout de 2 à 3 semaines de lavages du sinus maxillaire tous les deux jours cependant que le patient faisait lui meme un lavage à domicile selon Harke le liquide



1) Section of the incudostapedial joint The elastic fibres of the capsule appear black

Fig 2

2) Longitudinal section of stapedius muscle and tendon The elastic fibres appear black (After Harty)

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The fluid motion of the lymph which gives rise to these sense reactions, also exercises an intermittant pressure on the labyrinthine walls, like waves braking on the shore (5) The effect of waves in a closed system may be quite enormous and the pathological changes in the laby rinth of which hydrops is a part may well be explained as an action of such intermittant pressure from an abnormal fluid motion of the lymph

In the 4 patients in whom impedance was recorded, we found normal acoustic and tactile stapedius reflex, the latter being elicited by touching the homo and contralateral ear Thus indicates normal middle ear function eliminating the possibility of the mechanical" component being localized in the middle ear

What is the cause then of the apparently mechanical component in the low frequency area?

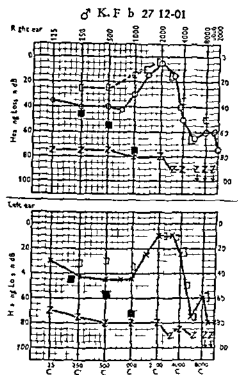


Fig 1

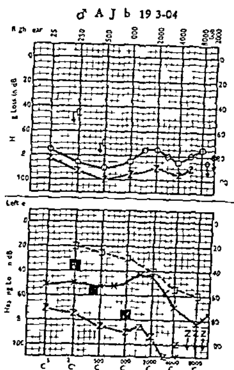


Fig 2

z—z Impedance threshold curve for air conduction stimuli
■—■ Impedance threshold curve for bone conduction stimuli

In individuals with normal hearing impedance changes cannot be produced by using the audiometric bone-conduction receiver This is due to inadequate out put, the acoustic impedance threshold not being reached.

I have been able to show in patients with comb ned mechanical neurological hearing loss in the low frequency areas, that impedance changes can be produced in both ears placing the bone conduction receiver on the masto d process The impedance threshold curve for bone conduction stimuli in these patients is thus, below that of persons with normal hearing This does not apply to frequencies exceeding 1000 cps Further there is a marked difference between the impedance threshold curve for bone and air conducted sound in the low frequency area.

These findings show that, in these 4 patients low frequency bone conduction stimuli must in some way stimulate the inner ear more than usual. Abnormally low impedance threshold curves for bone conduction st mul the presence of an apparently mechan cal component in the pure tone aud ogram and a cons derable d fference between impedance threshold curves of bone and air conduction are, therefore obta ned

Illustrative Case Reports

Case 270201 K F — A 6? year old man with Mb Men ère. Pure tone aud ogram (fig 1) shows an apparently mechan cal component in the low frequency areas On record ng impedan e normal tactile intra aural reflexes are seen ind cat ng normal m ddle ear function At frequenc es

below 1000 cps the impedance threshold curve for bone conduction stimuli is abnormally low, with a distinct distance between this and the impedance threshold curve for air conduction stimuli

Case 190304, A J A 59 year old man with Mb Menière Impedance changes in both ears can be recorded on bone conduction stimulation, but only when the bone conduction receiver is placed on the left mastoid process, and not when it is placed anywhere else on the head (fig 2) This might suggest that the left mastoid process prossessed some special features as far as sound transferrence is concerned However, the impedance threshold curve for bone conduction stimuli is situated at the limit of the audiometer's capability, and it is, therefore, impossible to determine whether applying a stronger stimulus to other sites on the head would result in changes of impedance

In the patients mentioned above all we can say definitely is that bone conduction stimuli in some way stimulate the inner ear more strongly than in persons with normal hearing This gives a) abnormally low impedance threshold curves for bone conduction stimuli in the low frequency area b) marked difference between the impedance threshold curves for bone and air conduction stimuli respectively, and c) an apparently mechanical component in the audiogram

Klockhoff

In connection with the papers that have just been given on the symptomatology and treatment in Menieres disease I would like to mention some general experiences gained from experiments that have been running for more than three years of long term treatment of this disease with dihydro chlorthiaxide Dichlotride, M S D (Klockhoff and Lindblom Nordisk Medicin, 67, 789, 1962) In a disease in which a chronic tendency for endolymphatic hydrops is considered to be an important pathogenetic factor it would seem appropriate to choose a well tolerated peroral diuretic, administered continuously, which acts on the electrolyte balance The summary account is facilitated by the distinction just made by Professor Opheim between the active and passive states of Menicre's disease

At first 30 typical cases were selected which after a comprehensive examination, were given Dichlotride 25 mg three times daily for six days a week over several months The patient group was arbitrarily selected with respect to age, and both active and passive stages of the disease were represented All the cases of the latter category — static flat loss of the perceptive type — remained unaffected whereas encouraging improvement were seen among the active cases — those of fluctuating low frequency loss of the perceptive type But on occasions there was a remarkably poor relationship between improvement and medication For instance, in one case there was a complete remiss on of all symptoms a few days after a two month period of treatment had been discontinued owing to the absence of any improvement It was thus evident that a possible effect of Dichlotride could be expected only in cases of the active type and that a very careful objectivization of the method was required to permit of reliable conclusions A double blind test was designed covering 30 typical active cases none of them more than 40 years of age — that is to avoid inclusion of changes dependent on aging All had thus only a low frequency loss of the perceptive type as an element in the familiar fluctuating syndrome triad By means of impedance recording of the acoustic stapedius reflex, it was confirmed that there was no component of conductive deafness and at the same time that all had the high degree of recruitment of loudness typical of Men ère's disease As earlier, the patients were initially admitted to hospital for a few days for audiologic neurologic and medical examinations But as a further step in the direction of objectivization this was never done in immediate connection with the first contact with the patient, but instead the patient was first given reassuring explanations as to the character of the disease and the nature of the individual syndrome was studied for a few weeks by frequent contacts For it would be expected that the patients would consult a doctor when the symptoms are most severe, and hence when there is room only for improvement In Menière s disease with its familiar psychomatic features one would in the absence of a preliminary study run a particularly great risk of including in the experimental series irrelevant spontaneous remissions which in a final statistical analysis, would tend to mask any specific effect of the medication

The treatment covered a period of 10 months comprising two four month periods, each with tablet X or Y, in random order, three times a day, six days a week separated by a 2 month pause in the treatment Throughout the experiment there was regular contact with the subject and diverse tests were performed moreover contact was maintained with the patient even when the series was completed

An investigation of the described type is inevitably time-consuming and some data remain until the key to the blind test can be revealed and statistical analysis performed Hence no final results can be reported It may however be justified to stress the particular difficulties associated with therapeutic experiments on cases of Meniere s disease, and to describe our way of minimizing the risk of misinterpretations An interesting observation might be mentioned even now after the experimental series the syndrome almost invariably showed a less severe course than before the treatment had begun It is probable that we are here concerned with the psychosomatic phenomenon of reassurance

Holmgren to Eimind

The gap between air and bone curve in perceptive low frequency hearing loss can well be explained by the distortion which even in good bone receiver constructions amounts to a least 10 per cent If the audiometer is set at frequency 250 c p the bone receiver does not only produce the 250 c/s tone, but also a series of overtones of which the second and third (500 and 750 c/s) generally are the strongest The sensitivity of the ear is not a linear function of frequency as might be expected when looking at the rectangular audiogram The sensitivity for frequency 750 c/s is so much greater than for 250 c/s that the patient will hear the tone 750 well above the corresponding value for the air conduction receiver the distortion of which is insignificant. For this reason the audiogram will give the impression of the presence of a conductive component These circumstances have also been described by Groen Audiological aspects of Menière's disease Nederl. T Geneesh 106 1365 1962

Arnvig to Hansen

Before and after the publication of the remarkable cases of Hallpike and Cairns several temporal bones from patients who had suffered from Meniere s disease had been histologically examined without the finding of a dilatation of the cochlear duct.

Thus two cases were published from the laboratory of the Kommunehospital in Copenhagen (Videbech 1935, Arnvig 1947) A special feature of these cases namely a pronounced compression of the organ of Corti was demonstrated

In several of the cases to be published later confirming the finding of Hallpike and Cairns a similar "compression" of the organ of Corti was seen

The same phenomenon is present in the case demonstrated to-day by C. C. Hansen By the school of S H Mygind it is characterized as endolymphatic compression" and assumed to be caused by an increased fluid output

According to Mygind the cochlea in the mild cases of Meniere s disease and perhaps the reversible ones may show the endolymphatic compression as the only finding whereas the more pronounced cases reveal both the compression of the organ and a dilated duct

Jan Stahle

Hydrochlorothiazide in the treatment of Meniere s disease

According to numerous concurring reports about 75 % of all patients have been freed from or improved with respect to vertigo through medical treatment of various sorts. For the remaining 25 % one of the several types of operative approach is called for (Cawthorne, 1959) The results of medical treatment are good and the selection of which medication or cure can therefore be a matter of choice

In the majority of reports, the treatment for vertigo alone has been evaluated, while the effect on the hearing is ignored

If one accepts the theory that Menière's disease is caused by a disturbed vasomotor function which leads to a periodic accumulation of fluid and/or salt in the inner ear, there is good reason to treat with diuretics This idea was launched as early as 1931 by Dida Diderding

In conjunction with Norell, I have since 1958 treated a great number of cases of Menière's disease with hydrochlorothiazide (Stahle, 1959, Norell & Stahle, 1961, 1962) We have here used ESIDREX® and ESIDREX K® (CIBA) given in courses of 1—3 weeks The results of the treatment have been evaluated mainly with regard to hearing (Table I) Pure tone audiograms before treatment and after an observation period of 1/2—2 yers have been compared The first audiogram has often been taken towards the end of an attack of vertigo with its resultant hearing reduction

From Table I, it can be seen that an improvement in hearing more often occurs in recent cases (duration of sickness up to 2 years) compared with long standing cases (> 2 years) We have interpreted this hearing improvement as indication of spontaneous remission

We attach considerable importance to the observation that the hearing was not worsened in 63 out of 65 cases during the observation period This can be expression of a dehydrating effect on

Table I *Hydrochlorothiazide treatment in Menière's disease*

	65 cases	*Observation time 1/2—2 years*
Hearing	Improvement (10 db) in	80 % recent cases 40 % longstanding cases
Vertigo	Improvement in 75 %	
Vestibular function	Normalization in 40 %	
Of special interest	No further hearing loss in 63 out of 65 cases	

the inner ear We believe that diuretics can protect the inner ear from irreversible lesions and thereby prevent additional damage to the hearing

With respect to vertigo — we have seen improvement in 75 % of our cases We are of the impression that hydrochlorothiazide administered during the pre vertiginous aura could impede or prevent the attack.

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Neergaard to Eimind

In connection with the paper Mechanical component to deafness in Menière's disease' some experimental investigations appear to be of interest The influence of increased hydrostatic pressure in the cochlea upon the transmission of sound in specimens of the human temporal bone was investigated by G v Békesy (1942, 1949, 1960) The finding that no change in the sound conduction can be measured even at pressures amounting to about 4 atm has been confirmed by H. C. Andersen et al. (1962)

GLOMUS TUMOURS S NONCHROMAFFIN PARAGANGLIOMAS OF THE HEAD AND NECK

By

Peter Berdal, Magnus Braaten Chr Cappelen jr and *Erling A Mylius*

From the Oto laryngological Department (Head Odd Opheim) Surgical Department A (Head Leif Efskind) Institute of General and Experimental Pathology (Head Leiv Kreyberg) University Hospital Oslo

The normal glomera or paraganglia in the head and neck may be grouped as follows

1 Glomus s paraganglion caroticum

2 Glomus s paraganglion jugulare tympanicum
   a in the adventitia of the jugular bulb along the nerves of Jacobson (IXth nerve) and Arnold (Xth nerve)
   b in the middle ear along the tympanic nerve (Jacobson)
   c along the auricular branch of the vagus (Arnolds nerve) in its course within the temporal bone, beyond the jugular fossa

3 Glomus s paraganglion vagale just beneath the jugular foramen within the ganglion nodosum (glomus intravagale) or closely related to this (glomus juxtavagale)

The histological structure of the glomus jugulare and glomus formations of the ear is like that of the carotid body (Guild 1953) The various paraganglia have been considered as homologous parts of a system consisting of nonchromaffin tissue and closely associated with the parasympathetic division of the autonomous nervous system (Watzka 1943 Lattes 1950, Guild 1953 a o)

The function of the glomera is not fully known The carotid bodies and aortic bodies are chemoreceptors sensitive to changes of the oxygen tension in the arterial blood and a marked drop in pO_2 may release an increased ventilation Possibly the chemoreceptors are sensitive to changes of the carbon dioxide tension and to changes in the pH too (Comroe Forster, Dubois Briscoe and Carlsen 1955) — A possible production of adrenaline or closely related chemical substance has been discussed by several authors without being proved (Christie 1933 Lattes 1950 Lever Lewis and Boyd 1959 Terracol, Guerrier and Guibert 1956) Zettergren and Lindstrom (1951) assume that the tympano-jugular glomera are rudimentary organs without any function — Noradrenaline pro- [illegible] noradrenaline to characteristic argentaffin cells — Argentaffin cells of identical

Table II *Tumours of the glomus caroticum and glomus juxtavagale*

ase	Sex	Age	Location	Symptoms	Duration prior to diagnosis	Treatment	Remarks
1	M	66	Glomus caroticum	Lump in the neck	1 year	Extirpation	Noradrenaline-adrenal ne pro dusing tumou malignant
2	M	42	Glomus caroticum	—»—	1 year	X rays	Tumour in right middle ear pr ably glomus tumour
3	M	40	Glomus caroticum	—»—	2 years	Extirpation Lymph node dis section	Malignant tumo with metastase
4	M	76	Glomus juxtavagale	—»—	2 months	Extirpation Lymph node dis section Postoperative X rays	Malignant tumo with metastase

growth Patient no 1 died from widespread intracranial invasion of the primary tumour In case no 3 a recurrence is observed 11 years after the operation However, the patient being 76 years of age, and in good general condition, refuses reoperation In case no 7 the tumour was erroneously considered to be a *carcioma, and postoperative X-ray treatment was given immediately* She died 10 months later from a brain abscess The temporal bone was necrotic, probably due to X ray damage Except in this patient the wound healing has been success ful in all cases

In case no 16 the tumour offers histological signs of malignancy with in vasive growth in the bone Irradiation therapy is planned We are awaiting the healing of the operation cavity The risk for bone necrosis will then probably be lessened (Capps 1958) — In case no 17 we think X ray treatment should be given supplementary, although we feel doubt about the benefit of this In spite of many reports of favourable results of irradiation treatment of glomus tumours without malignancy we find the question difficult to judge The growth is usually very slow, confer case no 2 in which the tumour of the middle ear was observed for 13 years prior to the operation and still the tumour was limited to the meso-tympanum and the external meatus

In 4 cases (Table II) the tumour was situated in the neck Prior to diagnosis the tumour was noted for a time of 2 months up to 2 years — Case no 1 was a carotid body tumour producing considerable amounts of noradrenaline and adrenaline During the operation the blood pressure increased from 140 mm Hg to 210—220—250 mm Hg when the tumour was handled or compressed This case is described separately (Berdal, Braaten, Cappelen, Mylius and Walaas 1962) In case no 2 also a carotid body tumour, the growth was erroneously interpreted as a malignant epithelial neoplasm Radical operation was attemped

but had to be abandoned due to heavy bleeding A full tumour dose of X ray was given, and the size of the tumour was considerably reduced One year later this patient underwent a radical mastoid operation for rightsided chronic otitis During the operation no evidence of tumour growth was found However, histological examination of the removed tissues disclosed a neoplastic infiltration, interpreted as glomus tumour A similar multicentric origin of glomus tumours has been reported several times, first by Lübbers (1937) Case nos 3 and 4 are decidedly malignant neoplasms, both with histologically verified lymph node metastases Malignant metastasing tumours originating from glomus caroticum and from glomus vagale are discribed (Pendergrass and Kirsh 1947, Donald and Crile 1948, Burman 1955) However, some authors are not willing to accept them as genuine malignant growths (Gastpar 1961) — The reason is lack of histological signs of malignancy in their cases In our case nos 3 and 4 we have found all signs of malignancy including histological evidence

As we succeded in demonstrating production of adrenaline-noradrenaline in case no 1, a search for a similar hormone production has been carried out in all later cases Six cases of ear tumours, and three other cases of tumour in the neck have been thus examined In one case only (case no 14, Table I) small amounts of adrenaline (3 5 microgram/gram) and noradrenaline 1 2 microgram/gram) were found

Based upon histological and histochemical findings and upon functional properties the following grouping of tumours may be suggested

1 Tumours with numerous cells containing argentaffin granules and with positive diazo reaction Hormone producing (Fig 1)

2 Tumours with argentaffin cells in small number and without positive diazo reaction Hormone production is questionable (Fig 2)

3 Angioma like tumours without argentaffin cells and with no hormone production (Fig 3)

Malignant growth (Fig 4), may take place in all groups The preliminary diagnosis of these tumours is based mainly upon clinical findings Important supplementary examinations are X ray including tomography, carotid angiography and retrograde jugularography (Gejrot and Laurén 1963) Search for increased urinary excretion of catecholamines and repeated blood pressure measurements are necessary

It is important to be aware of the possibility of a glomus tumour before operation If the tumour is already removed, the above mentioned examinations can no longer be carried out

SUMMARY

Twenty-one cases of glomus tumours in the head and neck are reported In 4 cases the tumour is considered malignant, two of them with definite histological signs Attention has been given to a possible production of catecholamines

Fig. 1. Numerous argentaffin cells in tumour with hormone production. Hexamine-silver × 160.

Fig. 2. Widespread single argentaffin cells (center) in tumour with questionable hormone production. Hexamine-silver. × 480

Fig 3 Glomus tumour of ordinary type with vascular pattern Hematoxylin erythrosin saffron × 160

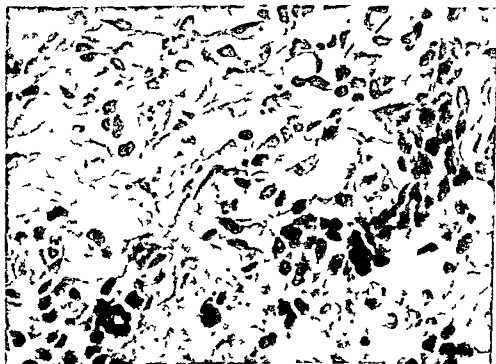


Fig 4 Malignant glomus tumour Some polymorphism can be recognized Hematoxylin-erythrosin saffron. × 160

Fig 1 Numerous argentaffin cells in tumour with hormone production Hexamine silver × 160

Fig 2 Widespread single argentaffin cells (center) in tumour with questionable hormone production Hexamine silver × 480

DISCUSSION

Braaten

I would like to make a few comments on the diagnosis of glomus tumours in connection with the paper which has been presented

I want to emphasize that the preliminary diagnosis must be based on a routine clinical examination Special examinations and tests are necessary to confirm or rule out the possibility of a glomus tumour In addition to regular X ray examination and tomography, we consider carotis angiography and retrograde jugularography, as demonstrated by Gejrot et al [1], of great value Of equal importance are repeated blood pressure measurements and examination of the urine for catecholamines

Differential diagnostic possibilities when the tumour is located in the tympano-jugular region include adenoma cylindroma, and carcinoma When the tumour is located in the neck, the most important differential diagnoses are branchial cyst hemangioma, tumours of the lymphoma group, lymph node metastasis, tuberculous lymphadenitis neurinoma, and lateral aberrant thyroid tumour

It is important to keep in mind the possibility of a glomus tumour before these tumours are operated on. A severe drop in the blood pressure during the operation may occur if the tumour has been secreting adrenaline or noradrenaline The analysis of the urine for cathecolamines is therefore of more than pure academic interest

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Fig 1 Survey picture from a glomus jugulare tumour taken with the electron microscope showing the picture with groups of tumour cells and thin walled capillaries Several small bodies in contact with capillary wall are presumably nerve endings

by thin walled sinosoid capillaries. These fourteen tumours thus were of the usual type according to Le Compte's classification.

Two tumours contained a right network of rather wide capillaries running between small irregular nests of somewhat spindle-shaped cells. These tumours were classified as angioma-like.

None of the three tumours tested for chromaffine reaction revealed any chromaffine granules.



Fig. 2 Survey picture of one tumour cell with large nucleoli in the nucleus and large number of small granules G and mitochondria in the cytoplasm

ELECTRON MICROSCOPY

The specimens from two nonchromaffine glomus jugulare tumours studied with the electron microscope were found to be dominated by round or oval epitheloid cells with oval nuclei. The cells formed clusters separated by thin-walled capillaries. Most of the cells seemed to be in close contact with a capillary resting with part of the plasma membrane on a thin basement membrane separating the plasma membrane of the epitheloid cell from that of the endo-

thelial cell In these areas the capillary wall was extremely thin and contained several pores of the same type as those found in the capillaries in the kidney tubules

Between some of the tumour cells were found secretory spaces that is thin tubular spaces without separate epithelial lining

The nuclei of the glomus jugulare tumour cells contained two or more nucleoli surrounded by dense clusters of chromatin The Golgi apparatus of the cells was found to be split into several small areas containing the typical smooth membranes surrounding thin *flat* spaces in the cytoplasm or vacuoles of varying size A large number of mitochondria of varying shape and size were spread throughout the cytoplasm

The most significant structure in the glomus tumour cell was a large number of dense granules 400 A — 300 A in diameter Each of these granules was surrounded by a membrane around 60 A thick which sometimes covered the immediate surface of the granule Sometimes however a thin light space was found between the membrane and the dense substance of the granule This was especially



Fig 3 Three neighbouring tumour cells meet in one point Observe large number of granules in two of the cells G rod shaped mitchondria and large oval nuclei part of which are shown in the picture

true for these granules located withın or close to the area of the Golgı apparatus These granules were also found to be less dense and somewhat more varyıng ın sıze than the other granules



Fig 4 The tumour cells rest on a th n basement membrane separatıng the plasma membrane of the tumour cell from that of the cap llary The cap llary wall ınd cated wıth arrows ıs less than 500 A ın most areas and full of pores covered w th a membrane less than 100 A thıck

DISCUSSION

The glomus jugulare tumours of the usual type appear very much lıke adenomas Mıtoses are usually not seen ın the specımens Most of the cells have the same sıze and the nucleı are regular ın shape and staınıng reactıon The well developed Golgı apparatus large nucleolı and close relatıon between the capıllary wall and the tumour cell suggests that the cell mıght have secretory functıon The pores ın the capıllary wall are of the type found ın relatıon to cells wıth secretory functıon Boyd et al (1951) demonstrated granules ın one glomus jugulare tumour The granules observed ın the present study ın two glomus jugulare tumours are very sımılar to granules observed ın sympathetıc nerve

endings (Grillo and Palay 1962) and in some heart muscle cells (Bloom 1962), which have been shown to contain large amounts of cathecolamines With these granules in mind it is interesting to notify that Lewer, Lewis and Boyd (1959) stated that several histochem al tests pointed to the existence of cathecolphenolic amine like adrenalin or noradrenalin or related substances in glomus tumor cells Berdal et al (1962) found noradrenalin in a glomus caroticum tumour from a patient who reacted w h blood pressure variations under surgical mani pulations with the tumou In on of the tumour cases described above with granulated tumour cells the cathe olam ne cor ent in the urine was tested and found to be normal It is alv a s difficult to relate morphology to function, and as we have not had the opportun ty to test the content of cathecolamines in the tumours studied we do not know whether hese tumours were cathecolamine pro ducing The similarity betwee the granules observed and known cathecolamine granules and the fact that ca h olamines have b en demonstrated in other tu mours of similar type seem to ake justi ied, hov ever an assumption that the



Fig 5 High magn fication of one area of a tumour cell show g the typ cal structure of the tumour granules with a dense central area surrounded by a thin less dense layer and a peripheral membrane around 60 A th ck Some of the granules appear in close relation to the flat mem brane-covered spaces of the Golgi apparatus.

tumour cells have secretory function and that the granules observed are related to production of cathecolamines presumably adrenaline or noradrenaline from the cells

SUMMARY

Sixteen tumours from the temporal bone classified as glomus jugulare tumours were studied in the light microscope Fourteen were of the usual type, two were angiomatous None of three tested tumours showed positive chromaffine reaction Specimens from two tumours studied in the electron microscope contained a large number of granules similar to those found in cathecolamine producing cells It is suggested that glomus jugulare tumours of the usual type are adenomas with the capacity to produce cathecolamines

Abbreviations

G Granulus typical for the tumour cells M Mitochondrion GA Golgi apparatus CA Capillary E Endothelial cell T Tumour cell N Nucleus Nu Nucleolus NE Nerve ending? 1 micron indicated with black line at the bottom of the picture

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RETROGRADE JUGULAROGRAPHY

A DIAGNOSTIC AID BY JUGULAR FORAMEN TUMOURS

By

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Stockholm

On the assumption that pressure on the nerves within the jugular foramen will also affect the internal jugular vein, which is situated just behind the nerves, a special form of phlebography of the internal jugular vein, retrograde jugularography, has been developed and tested at Karolinska Sjukhuset as a diagnostic aid in cases of syndroma jugulare The tumours or other growths that exert pressure on the nerve may be intra or extra-cranial or situated in the foramen itself The method and some typical cases, above all glomus jugulare tumours, are presented

RECONSTRUCTION OF EAR CANAL AND MIDDLE EAR IN CHRONIC OTITIS

By

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The operative treatment of chronic otitis media confronts us with several problems The first and foremost obviously is to eradicate infection from the middle ear and mastoid, and safeguard the patient against possible complications due to chronic otitis The second task is to repair the remaining sound conduction system or tho build a new one for better postoperative hearing Thirdly, the ear canal and middle ear should if possible, be reconstructed to their original shape without creating a cavity liable to frequent postoperative trouble

Total eradication of disease demands much more on the part of otologists than is commonly realized Although the mastoid segment generally is satisfactorily handled, the area around the labyrinthine block, the epitympanic recess, and the cells adjoining the Fallopian canal at its distal course, together with tympanic pathology, is often treated in amateur fashion leaving diseased tissue behind It is only by thorough study of the temporal bone that competent handling of these areas can be learned

The eradication of disease should be performed sufficiently radically even at the expense of the sound conduction system The incus and head of the malleus should be removed if they are grossly eroded, or if cholesteatoma membrane is seen to creep behind the ossicles If cholesteatomatous remnants cannot be totally removed, no closed reconstruction should be made The use of present day prosthetics generally allows one to make an effective reconstruction if only disease can be eradicated

Obliteration of the mastoid segment in simple mastoidectomy is no problem the musculoperiosteal flap advocated by Popper in 1935 has been in use in this clinic for more than 15 years and there have been no unfavorable reactions after occlusion of the mastoid antrum and cavity The problem to be solved was rather how to combine the reconstruction of the normal ear canal and tympanic membrane with the obliteration operation in the presence of chronic otitis

In chronic ears in children, cavity obliteration was done for many years as a routine operation, since creation of an open cavity in this age group is most undesirable Only tympanic reconstruction was left undone, the bridge and the bony posterior ear canal wall were removed, and the musculoperiosteal flap provided a well nutritioned bed for rapid healing of the ear canal skin

The introduction of fascial grafts in tympanic surgery led to the present

operative method which allows primary reconstruction of the ear canal and tympanic membrane simultaneously with musculoperiosteal occlusion of the cavity

The technique employed at present consists of retroauricular incision and formation of a rather long and broad musculoperiosteal flap, attached

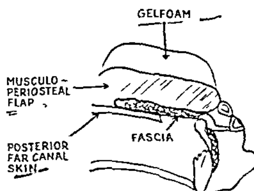


Fig 1 A schematic representation of the reconstruction operation The fascial graft is used to repair the tympanic defect as well as to close the gap between the membrane and the ear canal skin. Mastoid cavity obliteration is accomplished with the musculoperiosteal flap

to the posterior ear canal soft tissues Exenteration of the mastoid pathology is done in thorough fashion, paying special attention to the labyrinthine block The bridge is removed and the bony posterior ear canal

operation

under the drum and over the reconstructed chain An antiseptic vaselin gauze strip in then introduced into the meatus and placed over the new gelfoam-covered fascial drum The gauze strip smooths the ear canal skin nicely and shifts it into its natural position, a gap remains, however, at the annular region This gap is closed by lifting the remaining thicker part of the fascia upwards, to lie on the posterior side of the ear canal skin Placing of the musculoperiosteal flap against the fascia and ear canal skin completes the reconstruction operation

If the drum is totally missing it has been found better to lift the anterior ear canal skin from the annulus upwards, and to place the anterior end of the fascia

over this bare bone and replace the skin over it This gives the new drum a higher starting level and it does not become so easily fixed to the promontory as when the fascia is tucked under the annulus

The epidermis covering the remaining part of drum and ear canal should be respected, because it gives an excellent start for the ingrowth of epidermis over the fascial graft This occurs in a matter of days and fixation of the graft to the framework of the tympanic membrane occurs early I do not employ fascia over the drum since then obviously the epidermis should be removed from a large bed for the new graft It should be emphasized, however, that the tympanic part of the fascial graft should by very thin Thick grafts tend to leave a shallow tympanum, and there have been no nutritional fascial perforations in the whole three-year series

This series includes 29 ears in which no tympanic reconstruction was made because of extensive pathology at the tympanic recess and because the Eustachian tube was closed In some of these the promontory epithelium was removed and allowed to derive its new covering from the annular region In other cases a thin piece of fascia was laid on bare bone so as to adhere to it with subsequent epidermization The latter method seems to lead to quicker healing and is routinely employed at the present time In all cases closure of the radical cavity and reconstruction of the meatus was done in the usual fashion with success The hearing level did not come up to 30 db in any of these cases but generally remained at, or improved to, 40—50 db

We now attempt reconstruction of the ossicular chain in all cases in which a new, closed tympanum is created Window plasty has been adandoned Suitable pieces of polyethylene tube can be made to connect the malleus handle to the stapes, or to the footplate, or an umbrella-shaped stapes is connected to the fascial drum If the drum is totally missing and only the footplate remains, I employ a polyethylene columella lying on the side, one long side arm connecting it to the footplate (Fig 2) The results with artificial prostheses have been clearly better than those of window plasty

Primary reconstruction of the drum and ear canal are possible in a great majority of discharging ears As pointed out earlier, conservative treatment with special emphasis on local aural toilet, together with several cultures and sensitivity tests should never be omitted in the preoperative work-up Systemic treatment with proper antimicrobial agents greatly enhances the chances for rapid

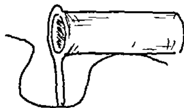


Fig 2 The present method of columellization if both the stapes crura and the tympanic mem brane are absent. The polyethylene strut with a sidearm in the oval window niche keeps its place securely and transmits sounds from a new fascial drum to the stapes footplate

cure However *success cannot be hoped for if infected tissue is left behind during* surgery

If the invad ng organism is Pseudomonas pyocyaneus a strain of Proteus or Faecalis alcaligenes the preoperative treatment should be thorough to destroy most of these organisms and great care is needed in tympanic part of the surgery In experienced hands primary reconstruction can however always be attempted if tympanic pathology has been removed and the tube is open

RESULTS

The series operated on the lines described above consists of 180 ears the longest observation time being over three years Owing to the fact that these operations have also been made by less experienced members of the staff some complications have appeared mainly due to mishaps with the stapes and less frequently to the closed operation method as much These complications have been reported earlier and as less experienced surgeons are now allowed to do the operation only under supervision no further complications have been seen It should be stressed once more that the method is not suitable for any casual operator but only for those who regularly deal with chronic ear operations and can competently handle any type of ear pathology

The results as regards hearing obviously depend upon the aural pathology and the means of reconstruction Naturally the best results are obtained in cases with an intact pars tensa and tympanum with minor ossicle reconstruction In the case of total pars tensa defect the footplate only remaining the results obviously are not as good as when only the posterior part of the pars tensa is absent. The results in various reconstructive groups are shown in Table I

T a b l e I *Results in terms of hearing (re 30 db hearing level)*

Type of Operat on	Total Ears	Pract cally Useful Hearing	Per cent
Oss cular Chain Intact or Reconstructed	53*	35	66
Columellizat on	35	19	54
Artificial Stapes	31	13	42
Window Plasty	26	6	23
No Reconstruct on	29	—	0
Total	174**	73	42

* A fixed footplate in 5 ears
** Ears w th bone conduction level of 30 db or better

Postoperative discharge from the ear has occurred in 4 ears (2 per cent) permanently After one year 1 of these patients died from other causes and the other three have shown discharge only intermittently The results in this respect are greatly superior to open cavities of which at least 10 per cent show permanent postoperative discharge Those cases in which intermittent postoperative dis

charge occurred were, without exception, ears in which no reconstruction was made and in which the promontory surface was left bare

This operative method lends itself well to obliteration of old, discharging cavities The musculoperiosteal flap in these cases must be broader and longer than usual, the skin covering of the new meatus is partly derived from the cavity skin lining the proximal part of the musculoperiosteal flap, and partly from the areas around the Fallopian canal superiorly and inferiorly The ear canal should be kept open with the gauze strip longer than usual, about 3 weeks, to allow epithelialization of the flap as well as to yield a normal-sized rigid ear canal

SUMMARY

The operation of fascio-meato tympanoplasty combining primary reconstruction of the middle ear with cavity obliteration in chronic ear disease is described, together with some recent improvements The operation should be performed only by otologists with thorough training in aural surgery, as no disease can be left behind if the cavity is to be obliterated and the tympanum closed The results in hearing are presented, postoperatively only 2 per cent showed permanent drainage

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DISCUSSION

Palva to Kettel

Most of the various *musculoplastic flaps are subject to considerable post-operative atrophy* This is especially true if the pedicle is thin and narrow e g the flap used by Guilford and to some extent also in Rambo's flap In my [illegible] the broadest part of the lambeau, and p[illegible] not subject to later atropy If the cavity [illegible] ith gelfoam, or sometimes bring down a [illegible] in France prefer to fill the cavity with [illegible] ver, that my technique has the special advantage in keeping the ear canal skin as a whole tube and even if the cavity is large, the postoperative ear canal retains nearly its original size and the fascial graft receives quick epithelialization from the margins of the perforation

There have been 3 revisions at the immediate post-operative period because at one time, senior residents were allowed to do this operation without supervision

It must be stressed once more that the use of an obliteration technique demands an experienced ear surgeon. As to late complications, none have appeared, the oldest cases having an observation period exceeding three years

MYRINGOPLASTY

A 4 YEAR SERIES REVIEWED 2 YEARS AFTER OPERATION

By

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Abstract

4 years experience of myringoplasty operation with fascia graft is reported and analyzed.

During the last decade surgical repair of the middle ear for chronic otitis has been widely practised in various quarters, including Lund. We soon found, however, that the conventional methods with transplantation of skin or mucosal grafts did not produce satisfactory results. In 1957 we therefore tried to find a more reliable form of transplanation. A preliminary report of the results achieved was published in "Forhandlingar i Svensk Otolaryngologisk Forening 1958—1959". We found, among other things, that fascia would probably be a more suitable graft tissue for myringoplasty.

Today I should like to describe the results obtained in a series operated upon with *fascia during 1957 to 1961 and reviewed 2 years after operation*, and a small control series in which skin grafts were used. It should be pointed out that all patients who sought advice at the department because of chronic otitis were operated upon irrespective of the strength of the indications for surgery found at preoperative clinical examination.

METHOD

The preoperative examination was performed in the way described in the abovementioned previous publication with the exception that tubal function was not only examined by Politzer's, Valsalva's and particularly Toynbee's tests but also by a much more reliable test devised at our department. The surgical procedure does not differ essentially from conventional methods apart from the fact that fascia from the temporal muscle was used as a graft material. It should be observed that the loose connective tissue lateral to the thin, well defined fascia must be carefully removed and that the graft should be about 50 % larger than the surface it is to cover.

We chose fascia for several reasons. We know, among other things, that skin is more or less infected with various low-virulent bacteria, which normally produce no clinical symptoms. We also know that it is difficult to free the skin of these bacteria. Even mild infections of the graft and the bed are enough to lower the pH and, as known from the literature on plastic surgery, thereby jeopardize the fate of the graft. It is also known from this literature that it is not worth while to transplant epithelial cells because they do not survive and secondly that

the margins of such small grafts as those used for myringoplasty are readily invaded by epithelium It is also a commonplace that tissue poor in cells with a low metabolism is more likely to survive than a graft tissue rich in cells It should also be borne in mind that instrumental maltreatment of the graft should be avoided as much as possible Such manipulation can be reduced to a minimum by the use of preformed grafts of suitable thickness and not requiring instrumental trimming Fascia is sterile poor in cells with a low rate of metabolism and is available in suitable thickness over the temporal musculature

RESULTS

Myringoplasty with skin grafts in patients reviewed after 2 years

Of all together 19 patients operated upon successful takes and improvement of hearing were obtained in only 2 One might suspect that the failures were due to acute otitis with secondary perforation or to impaired tubal function But in 10 of these 17 failures tubal function was impaired and in none had acute otitis occurred

Myringoplasty with fascia grafts in patients reviewed after 2 years

Ninety two patients were operated upon Ninety of these were followed up for 2 years It was found that the graft had taken in 78 and that it had perforated in 12 Of the 78 cases in which the graft had healed in tubal function was good in 56 Of the 12 failures on the other hand tubal function was good in only 2 in which the perforation had occurred in association with acute otitis

Effect of operation on hearing

Of the 90 patients reviewed, conduction was impaired by 10 db or less in 70 while in 20 hearing was impaired still more and then the operation was regarded as unsuccessful as far as its effect on hearing is concerned Of those in whom hearing improved tubal function was good against only 2 of those in whom the operation failed to improve hearing In these 2 cases the drum was perforated in association with acute otitis after the operation

Tubal function in relation to fate of graft and hearing capacity after operation

Of the 58 patients in whom tubal function was good the drum had perforated and hearing had not been improved in only 2 in both because of acute otitis after the operation Of the 32 patients in whom tubal function was somewhat impaired the graft had healed satisfactorily in 22 while hearing was normal in only 12

DISCUSSION

The fact that the operation was successful in 56 of the 58 with good tubal function is but natural It is however remarkable that of 32 patients with impaired tubal function hearing was good in 12 and that in 22 the graft

healed in without subsequent perforation Two possibilities may be considered in the explanation of this favourable fate or the graft in these cases Firstly, at preoperative examination of tubal function there might have existed a functional stenosis which later disappeared in association with treatment of the middle ear (this has recently been observed after antioedemic treatment of the tube) and secondly, a normal sized functioning cell system may help to relieve the pressure We therefore now always measure the size of the functioning cell system pre operatively by a special method devised at the department

CONCLUSION

It was thus found that fascia is superior to skin as a graft material for myringoplasty, that in patients with good tubal function myringoplasty with fascia heals well and improves hearing in more that 95 % of all cases treated, that impaired tubal function may be due to functional obstruction that can be remedied, and that in the presence of functional tubal obstruction a large cell system may facilitate healing

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DISCUSSION

Hansen to Ortegren

51 cases of perforation of the ear drum were repaired with fascia The operations were performed without incision in the auditory canal using an operating microscope

Fascia from the temporalis muscle was obtained through a separate incision The transplant was covered with dry surgical packing which was left undisturbed for 1—2 weeks

Patients with manifest or suspected allergy were treated with dexametasone perorally 2 to 4 weeks postoperatively

Tubal function was tested by insufflation

Prothesis test according to Agnar Halls paper disc method was done on most of the patients preoperatively

The average age of the patients was 30 yea s the youngest being 4 and the oldest 72 years of age Their perforations had been present for from 4 months to 40 years on an average 15 years

Results

Of 51 cases 41 healed by primary indention — 82 %

4 cases healed after reoperation

3 cases with very small perforations of the transplant (less than 2 × 2 mm) healed after excision of the rim and covering with a small piece of meatal skin

Totally 48 out of 51 cases are healed — 94 %

Of 51 cases 42 were brought to the 30 db level — 84 %

On 3 cases an exploratively tympanotomy was done as a second operation

1 had otosclerosis and underwent a stapedectomy (Portman type) 2 had defects in the ossicular chain and were operated with interposition of incus between head of stapes and ear drum — even these patients eventually reached the 30 db level — totalling 88 %

This material confirms Agnar Halls experience — that myringoplastics can safely be done without incision in the auditory canal The author feels it is very important to treat all patients with suspected allergy with cortisone derivates for some weeks postoperatively

ELECTRONYSTAGMOGRAPHY BY MEANS OF AN ELECTROENCEPHALOGRAPH

(Simultaneous optic and electrical recording of optokinetic nystagmus with a view to determining the reliability of records obtained by electroencephalograph)

By

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The introduction of an electroencephalograph by which to record nystagmus involves several advantages Firstly, such instrument is generally available in large hospitals and hence no new apparatus need be purchased for a recording of nystagmus, secondly, electroencephalographs are provided with eight channels thereby making it possible to record simultaneously horisontal and vertical nystagmus individually in either eye If desired, the extra channels may serve for recordings of e g the cardiac or the cortical activity Special types of instruments permit a recording direct on the curve of the speed of the slow phase

The electroencephalograph used in the present study operates by alternating current amplifiers and consequently nothing but changes of voltage is recorded If the eye of the subject is moved, the pen will record an amplitude on the paper Even though the eye remains in the new position the pen will return automatically to the base line with a velocity which is conditional on the time constant of the amplifier In the following the time constant is set at 1 0 second, the object being to comply with the scale indications on the instrument and the instructions provided by the manufacturer, namely that the time constant is geometrically defined and not, as generally stated in the literature, arithmetically and commensurate with the interval lapsing until the amplitude has fallen to about 37 per cent of the initial value According to this latter definition the time constant for the encephalograph would be 0 7 second and not 1 0 second Any unambiguous picture of the eye movement is not obtained by an alternating current amplifier The higher the time constant used, the less marked the distortion of the curve obtained (Fig 1)

Aschan et al (1956) used an alternating current amplifier with a time constant of 1 7 second Hamersma (1957) used a time constant of 7—10 seconds Hallpike et al (1960) preferred to use a direct current amplifier, the advantage here involved being the recording at any time of the position of the eye But such amplifier is difficult to use because the problem of drift within the amplifier and electrical artefacts generated at the skin electrode interface

The electroencephalograph concerned (Kaiser) operates by alternating current amplifiers with time constants to be adjusted between 0 1 and 1 0 second, according to the scale of the instrument With a view to investigating whether

recordings of nystagmus obtained by this electroencephalographs adjusted to the time constant 1 0 second are applicable for calculations of the angular speed and thus is adequate in routine recordings of nystagmus and nystagmusresponse to rotatory, caloric, and optokinetic stimuli we have compared results obtained by such instrument with findings obtained simultaneously by optic recording

An "American Master Ophthalmograph was used for the optic recording

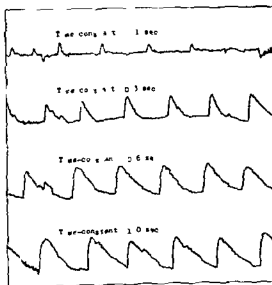


Fig 1 Optokinetic nystagmus recorded by electroencephalograph adjusted to different time constants

the principle of which is that a ray of light is directed to the cornea and subsequently reflected onto a film where it is marked as a dot If the eye is moving, a line is drawn indicating exactly the eye movement The instrument was demonstrated by E Holm Pedersen in 1949 at a meeting of the Danish Ophthalmological Society

H K Kristensen and K Zilstorff Pedersen (1953) used the ophthalmograph to determine exactly the duration of nystagmus in caloric tests ad modum Cawthorn Fitzgeral and Hallpike (1942) The investigators found fair correlation between the duration of nystagmus recorded optically and of nystagmus measured by direct observation

Hoffman, Wellman and Carmichael (1939) recorded the eye movements while subjects were reading, using simultaneously recording by ophthalmograph and alternating current amplifier These authors found the electrical recording highly satisfactory for the purpose

In the present study the ophthalmograph has been provided with a motor-driven drum (cf photo, Fig 2) on which a black, spiralformed line was painted While the drum is rotating an optokinetic stimulus will develop the angular speed of which is known If at the same time a couple of electrodes were fitted on both sides at the outer canthus and the nasal radix the eye movements would

be recorded simultaneously on the electroencephalograph and on the ophthalmographic film. A Kaiser electroencephalograph adjusted to a time constant of 1 0 second was used. The angular rates discussed below were calculated on the basis of direct measurement of curves.

Initially the drum was made to rotate so as to obtain a velocity of the spiral



Fig 2 (Photo) Motor-driven spiral drum fitted to an "American Master Ophthalmograph".

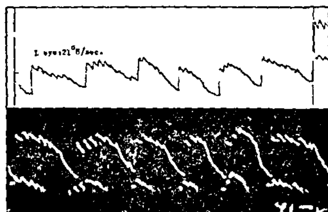


Fig 3 Simultaneous electrical and optic recordings of optokinetic nystagmus Uppermost curve electrical recording of movements of the left eye Lowermost curve optic recording of movement of the left eye

Experiment 1

Optokinetic stimulus		2[illegible] sec	25° [illegible]/sec	26° 0/sec	8° 7/sec	8° 7/sec
Optic registration	L eye	[illegible] 7 [illegible]	2[illegible] [illegible]/sec	22° 4/sec	8° [illegible]/sec	8° 7/sec
	R eye	1[illegible] sec	x	x	8° 4/sec	8° 5/sec
E n g registration	L eye	1[illegible] 2/sec	1[illegible] 8/sec	23° 0/sec	9° 4/sec	8° 8/sec
	R eye	§	§	§	7° 8/sec	7° 5/sec
	B temp	17° 0/sec	22° 4/sec	22° 8/sec	8° 6/sec	8° 6/sec
		Without instruction	Instructed to follow the stripes			

x Not readable light spot displaced outside the film

§ Not readable [illegible] disturbances

Fig 4

which corresponded to an optokinetic stimulus of 26 degrees per second In the first test the subject was instructed to look merely at the drum Thus a frequent nystagmus was obtained although the amplitude was low The angular speed was found to be 15° 7/sec using optic recording as opposed to the 17° 0/sec obtained by electroencephalographic recording

Were the subject told to observe closely the lines the nystagmus frequency would be lower but amplitudes higher, and the angular speed would be accelerated, optic recording showed 21° 8/sec, electrical recording 22° 4/sec When the experiment was repeated the same result was obtained (cf Figs 3 and 4)

When the optokinetic stimulus was reduced to 8° 7/sec the recorded angular speed would tally with the given stimulus Also this experiment showed agreement between findings by optic and electrical recording

Three other subjects were individually exposed to the experiments using optokinetic stimuli of 8° 3/sec Agreement was found also here between the optic and the electrical recordings (Figs 5, 6, 7 and 8)

Calibration before and after the introduction of the optokinetic stimulus was

Experiment 2

Optokinetic stimulus		8° 3/sec	8° 3/sec
Optic registration	L eye	7° 9/sec	x
	R eye	x	x
E.n.g registration	L eye	8° 2/sec	8° 4/sec
	R eye	8° 3/sec	8° 4/sec
	B temp	8° 1/sec	8° 7/sec

x Not readable light spot displaced outside the film

Fig 5

Experiment 3

Optokinetic stimulus		8° 3/sec	8° 3/sec
Optic registration	L eye	8° 0/sec	8° 1/sec
	R eye	8° 5/sec	8° 5/sec
E n g registration	L eye	8° 3/sec	8° 2/sec
	R eye	8° 1/sec	8° 2/sec
	B temp	8° 4/sec	8° 1/sec

Fig 6

made in all experiments with a view to providing against changes in the cornea-retina potential. According to expectation, and because of the brief duration of experiments (less than one minute) no changes were noted (Munthe Fog, 1963).

The speed of paper was in all cases 15 mm per second.

Thus the recording of eye movements by means of the electroencephalograph

Experiment 4

Optokinetic stimulus		8° 3/sec	8° 3/sec
Optic registration	L eye	8° 3/sec	8° 2/sec
	R eye	x	x
Eng registration	L eye	8° 2/sec	8° 2/sec
	R eye	8° 2/sec	8° 2/sec
	Bitemp	8° 1/sec	8° 2/sec

x Not readable light-spot displaced outside the film

Fig 7.

concerned is found to be sufficiently precise to be used, within certain limits, for measurements of the angular speed of the slow phase. It should be emphasized, however, that the experiments included angular speeds only between 8°/sec. and 22°/sec. Indeed, "the maximum eye speed" in most of the induced vestibular reactions will be found within this range. As emphasized by Aschen et al. (1956), in cases of spontaneous, vestibular nystagmus the speed of the slow phase will rarely exceed 10°, on rare occasions 20° per second. At a higher angular speed

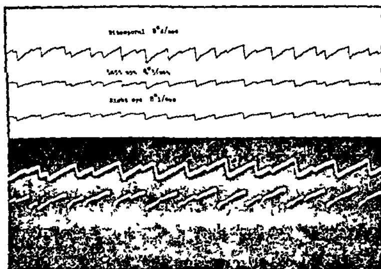


Fig 8 Simultaneous electrical and optic recordings of optokinetic nystagmus Uppermost curve. bitemporal electrical derivation Curve no 2 electrical recording of movements of the left eye. Curve no 3 electrical recording of movements of the right eye Curve no 4 optic recording of movements of the left eye Lowermost curve optic recording of movements of the right eye

than the one we examined, the time constant is of minor importance and will be correctly recorded At a very slow angular speed the values obtained by the here discussed electrical recording will probably be nearly at a minimum This feature is of less practical consequence, however, such type of nystagmus generally being qualitatively estimated

SUMMARY

Records of optokinetic nystagmus with angular speed between 8—22 degrees per second have been made simultaneously by means of an ophthalmograph and an electroencephalograph with a time constant of one second The angular speed as calculated from the records obtained by the two different methods have been practically identical According to this an electroencephalograph of the here discussed type can within certain limits be considered useful in most cases of electronystagmography

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DOLOMITE IMPLANTATION IN OZAENA AND ATROPHIC RHINOPHARYNGITIS

By

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Abstract

During more than six years dolomite rods have been successfully used as implants in cases of ozaena and atrophic rhinopharyngitis The operative technique and its indications are described

Since October 1956, a total of 120 submucosal implantations of dolomite have been made in cases of ozaena and atrophic rhinopharyngitis at the Turku and Helsinki University ENT departments The surgical treatment most widely used has been to narrow the nasal meatuses Insertion of implant material under the nasal mucosa has been favoured in the last few years Dolomite has properties which render it extremely suitable for this purpose It is one of Nature's minerals consisting mainly of calcium carbonate and magnesium carbonate and resembling bone in composition It is very well tolerated in the tissues The tendency to absorption varies in the case of different dolomites, but the dark dolomite quarried in Finland is practically speaking nonabsorbable Since this substance is well visualized in roentgenograms (Figs 1 and 2), the amount and site of the implanted dolomite can easily be determined roentgenologically

We have used dolomite as rod shaped pieces, 2—4 mm in thickness and 1—3 cm in length The pieces can easily be shortened or otherwise shaped with a file Under local or general anesthesia an incision is made in the skin of the nasal vestibule and pieces of suitable size are inserted submucoperiosteally into two wide pockets fashioned on both sides of the cartilaginous and bony septum (Fig 3) The incision is made on one side only and the subperichondral and periosteal pocket on the other side is made through an opening in the septal cartilage If the nasal meatuses are not too wide, this way of narrowing them is sufficient Otherwise additional pockets can be made in the bottom or lateral walls, usually on the upper side of the inferior turbinate, of the meatuses These pockets should be large enough to allow displacement of the mucosa towards the nasal meatus when the dolomite pieces are in position It may be advisable to perform the operative narrowing of the meatuses in stages Thus for example, application of the dolomite pieces to the septum can be made first After this the result may be watched for a couple of months and, if an additional operation seems necessary, the procedure can be completed by inserting dolomite into the bottom and, or lateral walls of the meatuses

This additional operation can be done on both sides at the same time, but often it is good to make the narrowing operation first on one side only and treat the

other side some time later This manner of proceeding has the advantage that the patient's nose does not become blocked on both sides at the same time After the operation there is almost always swelling of the nasal mucosa on the operated side which causes blocking of the meatus for a couple of days Should



Fig 1 Dolomite rods implanted in nasal septum

a meatus become too narrow after such an operation it is easy to widen it again by removing one or more dolomite rods

The meatuses are to be narrowed selectively, which means that the degree of narrowing must be greater where the meatuses are wider, and the aim should be to create a meatus of normal shape and width

The dolomite rods must not be placed so that they prevent puncture of the maxillary sinuses

Speaking of the results of these operations it should be said that implantation of dolomite rods means narrowing of the nasal meatuses — it does not cure the disease itself But this operation helps the patients in many ways This is clearly due in part to the fact that the narrowing of the meatuses results in recovery of the mucous membrane (Figs 4 and 5) The meatuses become cleaner and the foul smell and headache disappear

Some patients have complained of a blocked nose in cases where the meatuses



Fig 2 Dolomite rods implanted in nasal septum and into bottom and lateral walls of the meatuses



Fig 3 Dolomite rods in operatively created pockets on both sides of nasal septum.



Fig 4 Nasal mucosa of inferior turbinate before operative narrowing of meatus by implantation of dolomite rods. Metaplasia of mucous membrane to squamous epithelium.



Fig 5 Nasal mucosa of inferior turbinate some months after operative narrowing of meatus. Recovery of mucous membrance, which is again of normal appearance.

are narrowed too much Otherwise no complications or trouble have occurred in connection with this operation The sense of smell of ozaena patients is often very bad Unfortunately this operation has improved it in a few cases only

Dolomites has also been used for narrowing the nasal meatuses in cases in which their excessive width had caused atrophic rhinopharyngitis, though there was no actual ozaena The results were good in these cases too

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VASCULAR REACTIONS ON THE INTAKE OF FOOD AND DRINK OF VARIOUS TEMPERATURES

By

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Many investigations have been reported on peripheral vascular reactions resulting from exposure to external heat and cold, but only few on the corresponding reactions associated with the intake of food and drink of various temperatures

Pickering (1932) showed calorimetrically that the transfer of heat from the hand decreased when water at a temperature of 20° C was administered through a gastric tube When the water temperature was 46° C there was a progressive increase in the transfer of heat from the hand after a short latency With water at 37° C no change was observed in the blood flow of the hand. When water was circulated through a tube in the oesophagus without passing into the stomach there was a transient decrease in heat transfer from the hand at water temperatures of 20° C and 48° C

Dail & Moor (1938) found that the drinking of water, at all temperatures studied, resulted in a decrease in arm volume, indicating vasoconstriction The decrease was greatest when cold water (9° C—12° C) was drunk, it was also obvious with warm water (42° C—55° C), but was only slight when the water was at body temperature Vasoconstriction also occurred when warm or cold water was administered through a gastric tube, while the injection of water at a temperature of 37° C through the tube had no effect on the volume of the arm The reactions occurred regardless of whether or not the tube was insulated When the quantity of warm water supplied through the tube was 500—800 ml there was an increase in the volume of the arm following the initial decrease, and this was considered to be due to the relatively large amounts of heat supplied

Further studies of vascular reactions on the intake of water of different temperatures seem of interest The present communication reports studies of the blood flow in the skin, muscle and nasal mucosa following the intake of food and drink of different temperatures.

MATERIAL AND METHODS

The experiments were performed on 11 male and 10 female healthy subjects of ages 19—36 years. None of them had eaten, drunk or smoked for the four hours preceding the commencement of the experiments The subjects, dressed in ordinary clothes, sat with each arm resting on a board The temperature of the room was 23° C (± 1° C)

The thermal conductivity of the skin was recorded from the terminal phalanx of the middle

finger, and in the nose on the septal mucosa The measuring plates were connected to a Fluvograph (Hartmann & Braun) and the measurements were made as according to the method described by Hensel & Bender (1956) The plate in the nose was secured by a rubber balloon inflated to a pressure of 20 mm Hg no local anaesthesia was used in the nose In some experiments the thermal conductivity was recorded in the brachio-radialis muscle from a thermal conductivity probe (Hensel 1954) The skin was anaesthet zed with 1 ml 1 % Xylocaine without exadrine® before the introduction of the probe

The subjects were given waten in three different ways (1) they held water in the mouth for a few seconds and then spat it out, (2) 50 ml of water were then injected through a plastic tube (4.3 mm in diameter) into the stomach and (3) they swallowed two gulps of water (about 25—30 ml) Water at three different temperatures viz 37° C, 70° C and 4° C, in that order of sequence, was administered by each of the three ways The two extreme temperatures were chosen because they differ similarly from the body temperature and also because 70° C was found to be an average initial temperature of coffee when drunk. In a few experiments water at temperatures other than those mentioned was used and in some experiments the investigations were complemented by the administration of larger quantities of water (200—500 ml) e ther by drinking or injection into the stomach through a tube On a few occasions warm or cold food was also given, semolina porridge or ice cream being chosen respectively, since these foods require no chewing and as far as is known contain no ingredients with a pharmacological effect on the blood vessels The administration of all food and drink was performed by the person supervising the experiment, so that the subjects should not move their arms The water was drunk or sucked into the mouth by means of a curved glass tube

In one experiment 200 ml of water at a temperature of 4° C was circulated through a tube in the oesophagus The tube which was closed at its lower end contained a narrower tube extending nearly to the closed end and through which the water could flow out. In a separate experiment measurements were made while a rubber balloon in the oesophagus was filled with water and air

Finally in most of the experiments measurements were made of the blood flow of the hand with venous occlusion pletysmography according to the method described by Graf & Westersten (1959)

RESULTS

Because of the spontaneous variations in the blood flow of the finger and nasal mucosa, only relatively pronounced changes in the thermal conductivity occurring shortly after the administration of water or food were considered as caused by the administration

Almost all unequivocal changes in the blood flow of the nasal mucosa or the finger occurring after the administration of water were decreases In the experiment illustrated in Fig 1, the blood flow of the nasal mucosa and the finger decreased when the subject held water in the mouth for a short period, regardless of whether the temperatı re of the water was 37° C, 70° C or 4° C

In most of the experiments in which the recordings were not disturbed by artifacts during the introduction of the gastric tube, this resulted in a temporary decrease in the blood flow of the finger and nasal mucosa (Figs 1 and 2) An increase in the muscular blood flow occurred in a few experiments on the introduction of the tube (Fig 2)

The administration of water through the gastric tube resulted relatively often in a decrease in the blood flow of the finger and nasal mucosa, which was observed at all water temperatures tested In the experiment illustrated in Fig 2

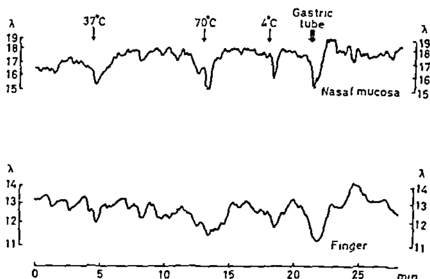


Fig 1 Continuous recording of the thermal conductivity of the nasal mucosa and finger (expressed in 10^{-4} cal · cm^{-1} · sec^{-1} · °C^{-1}) when the subject held water of different temperatures in the mouth for a few seconds without swallowing it, and also when a gastric tube was introduced.

the blood flow of the nasal mucosa decreased when either warm or cold water was introduced through the gastric tube, but was not affected by water of body temperature, while the blood flow of the muscle increased somewhat with all three temperatures.

The blood flow of the finger sometimes decreased when water at all temperatures tested was drunk (Fig 3) The reduction was greater and of longer dura-

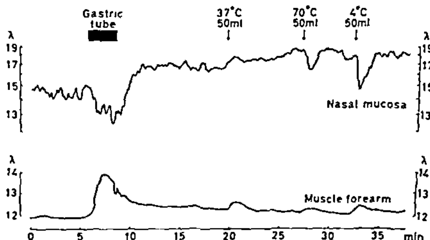


Fig 2. The thermal conductivity of the nasal mucosa and lower arm musculature on the introduction of a gastric tube and the administration of water of different temperatures through this tube.

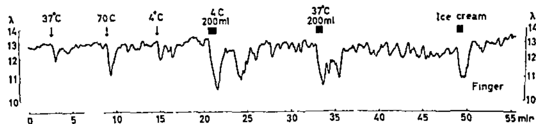


Fig 3 The thermal conductivity of the finger on the drinking of water of different temperatures and in varying quantities, and the eating of ice cream at a temperature of —5° C At each arrow two gulps of water of the temperatures shown were drunk

tion when larger quantities of water were drunk, this is shown in Fig 3 for water temperatures of 4° C and 37° C The changes in the blood flow of the nasal mucosa in a subject who drank water at 37° C, 70° C and 10° C are shown in Fig 4 At all three temperatures the blood flow decreased, though there was some latency of response The cold water gave rise to a prolonged decrease in the blood flow, while the warm water resulted in a transient decrease followed by an increase Similar observations were made on a few occasions as regards the changes in the blood flow of the finger after the administration of cold and warm water respectively

Fig 5 shows schematically the number of occasions on which a change in the blood flow of the finger, nasal mucosa and muscle was recorded in connection with the administration of small quantities of water of different temperatures and by different means The changes in the blood flow observed when large

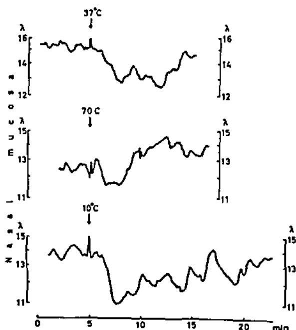


Fig 4 The thermal conductivity of the nasal mucosa on the drinking of two gulps of water of different temperatures The same subject in all three recordings

Mode of administration	Water in mouth			Water by gastric tube			Drinking		
Temperature °C	37	70	4	37	70	4	37	70	4
Finger n 14 (drinking 15) ↑									
Finger ↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓	↓↓↓
Nasal mucosa n 17 ↑		↑↑		↑					
Nasal mucosa ↓	↓↓↓	↓↓	↓↓↓↓	↓↓↓↓	↓↓↓↓↓↓	↓↓↓↓↓↓	↓↓↓↓↓↓↓↓	↓↓↓↓	↓↓↓↓↓
Muscle n 9 ↑	↑			↑	↑	↑			
Muscle ↓									

Fig 5 Diagram showing the changes in the blood flow of the finger nasal mucosa and lower arm musculature recorded while small quantities of water of different temperatures were either held in the mouth administered through a gastric tube or drunk The downward pointing arrows indicate a decrease in the blood flow, and the upward pointing arrows an increase For each measurement site the number of subjects investigated are given (In one experiment in which the blood flow of the nasal mucosa decreased when cold water was drunk the temperature of the water was 10° C instead of 4° C.)

quantities of water of different temperatures were given are not included in the figure As may be seen, the blood flow was affected comparatively rarely There was usually a decrease in blood flow of the nasal mucosa and finger On only three occasions was an increase in the blood flow of the nasal mucosa recorded, in two of the cases the change occurred when the subject took warm water into the mouth, and the increase in thermal conductivity remained high for long periods without showing any tendency to decline — it is therefore possible that there was an artifact change of base-line in the recording In one of these two cases the blood flow of the finger was measured and found to decrease In the third case a transient increase of nasal mucosal blood flow occurred after the introduction of water of body temperature through a gastric tube In no case was there *any increase in blood flow in the finger directly associated with the administration of water*

The blood flow of the finger changed less often when water was drunk than when it was held in the mouth or administered through a gastric tube The drinking occurred at the end of the experiments, when the thermal conductivity *of the finger was usually lower than when the experiment began* Plethysmographic measurements of the blood flow of the hand at the end of the experiment showed that on an average the blood flow was below 2 ml/100 ml min In the subjects who already had cold hands at the beginning of an experiment, the blood flow of the finger did not change on the administration of water during any part *of the experiment, and neither was the blood flow of the nasal mucosa usually* affected

Only in one experiment did the blood flow of the lower arm musculature change on administration of water and in this there was an increase both when water at all three temperatures was injected through the gastric tube (Fig 2) and *when the subject held water of body temperature in the mouth*

When large quantities of water of different temperatures were given as a drink or through a gastric tube, the blood flow of the nasal mucosa or finger

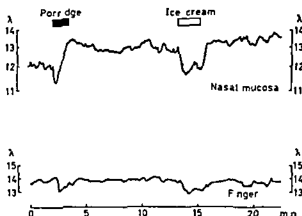


Fig 6 The thermal conductivity of the nasal mucosa and finger on the eating of porridge (+62° C) and ice cream (—14° C)

sometimes decreased also in experiments in which corresponding administration of smaller quantities of water of similar temperatures had produced no reaction, and in other experiments the decrease was more pronounced after the administration of a large than a small quantity of water (Fig 3) When relatively large quantities of warm water were administered, the initial decrease in the blood flow was sometimes followed by an increase

In the experiment in which 200 ml of cold water were circulated in a tube introduced into the oesophagus, no change occurred in the blood flow of the nasal mucosa or lower arm musculature, although the administration of cold water through a gastric tube in the same subject had resulted in a decrease in the blood flow of the nasal mucosa and an increase in that of the muscle, as shown in Fig 2 The subject had a feeling of coldness in the thoracic and epigastrial regions respectively on these two occasions

In four of six experiments the eating of ice cream resulted in a decrease in the blood flow of the nasal mucosa or the finger, or both (Figs 3 and 6) In one of three experiments the blood flow of the nasal mucosa and of the finger decreased temporarily when the subject ate warm porridge and then increased in the nasal mucosa to values exceeding the initial values (Fig 6) No change in the blood flow occurred on the eating of ice cream or porridge in the other experiments

On several occasions the subjects were asked to swallow air during the ex-

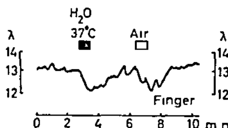


Fig 7 The thermal conductivity of the finger measured when a balloon introduced into the oesophagus was filled with water and air respectively

periments In no case was any effect observed on the blood flow of the nasal mucosa or the finger

In the experiment in which a thin walled rubber balloon lying in the oesophagus was filled with water of body temperature and then with air, the blood flow in the finger decreased on both occasions (Fig 7)

DISCUSSION

The results of this investigation confirm the observation made by Dail & Moor (1938) that the drinking of cold or warm water or its administration through a gastric tube may result in a transient decrease of the peripheral blood flow and that a decrease may also occur on the drinking of water of body temperature In contrast to their results, a decrease in the blood flow was also sometimes observed in the present investigation when water of body temperature was given through a gastric tube This reaction occurred both in the skin of the finger and in the nasal mucosa, and was also observed on the intake of warm or cold food Even when water was taken into the mouth and then spat out, the blood flow of the finger and nasal mucosa sometimes decreased

This decrease in the blood flow of the finger and nasal mucosa when water was taken into the mouth or administered through a gastric tube, or when water or food of varying temperatures was swallowed, can hardly be a typically thermically provoked reaction in the peripheral vessels, since a decrease in the blood flow also occurred on the administration of warm water or water of body temperature In the experiment in which cold water was allowed to circulate in a tube in the oesophagus, the blood flow of the nasal mucosa did not change although the subject had a feeling of coldness in the mouth and in the lower thoracic region

The swallowing movements in themselves could not have been the provoking factors either, since no reaction was shown when the subjects ' swallowed drily ', and the reaction also occurred when water was held in the mouth but not swallowed

The question arises whether the reaction is due to a central nervous "arousal ', in some way evoked by the procedure The blood flow of the finger and nasal mucosa often decreased when the gastric tube was being introduced, and it is possible that the mechanical contact with the mucosa in the upper alimentary canal constitutes the triggering factor in the reaction of the peripheral blood flow on the administration of water or food The fact that the reaction was often more pronounced on the administration of large than small quantities of water, even when the temperature of the water was 37° C or higher, supports this hypothesis It is also supported by the decrease in the blood flow of the finger on the inflation of an oesophageal balloon The results of this investigation indicate that the reaction may be provoked from the mouth, oesophagus or stomach

This investigation cannot answer the question regarding the pathways involved in the reaction which results in a decrease in the blood flow of the finger

MEDIASTINAL SARCOIDOSIS

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Although there are somewhat divergent views on the nature of sarcoidosis, most workers regard it as a clinical entity which can be differentiated from a small number of diseases giving similar histological changes (Uehlinger, James, Lofgren 1961) For the diagnosis of sarcoidosis, in addition to the clinical picture, histologic evidence of sarcoid tissue should be procured as far as possible This has been obtained most often from the supraclavicular lymph nodes or from the bronchial mucosa In extrapulmonary sarcoidosis, skin biopsies, peripheral lymph node biopsies, liver puncture, bone marrow puncture and skeletal muscle biopsies may reveal evidence of sarcoid involvement of the tissues

Both Uehlinger and Lofgren emphasize that in the clinical diagnosis, the pulmonary involvement is essential Uehlinger states further that, during the progression of the pulmonary disease, the lesions manifest themselves in various organs, viz skin, reticulo endothelial system salivary and lacrimal glands, chorioidea, and skeletal and heart muscle The difference from tuberculous spread is also here distinct, the latter favors the meninges, the skeletal and urogenital systems, and the joint capsules Lofgren stresses, however, that if extrapulmonary local sarcoid lesions are demonstrated histologically in the absence of characteristic clinical pulmonary involvement, the case should not be labelled sarcoidosis

It is generally agreed that sarcoidosis occurs in two different forms, the acute or subacute, and the chronic form The former is often characterized by the appearance of erythema nodosum, generally followed of bilateral hilar adeno pathy This glandular enlargement is clinically good natured and tends to disappear in about a year It is seen most frequently in young adult women during the third decade The chronic form is seen in a somewhat older age group, hilar adenopathy is then less marked and pulmonary mottling more pro nounced The lesions heal by fibrosis, spontaneous remissions are rare, and prognosis poor Histopathologically the first form is characterized by typical epithelioid and giant cells tubercles without caseation, the latter manifests itself in hyalinization of the foci resulting in intensive scar formation and deformation of the surrounding structures (Uehlinger)

The subacute form has been found to be much more frequent than it was thought earlier Mass miniature radiography has focussed attention on cases of hilar adenopathy often otherwise unsymptomatic In a Stockholm survey Lofgren gives the incidence in the highest age group (25 to 29 years) as 9/10 000 for males and 11/10 000 for females Similar figures have been obtained in the New York area (Hirsch 1961)

Until recently the only method of obtaining suspected glandular tissue for biopsy in cases of pulmonary sarcoidosis was by means of scalene node (Daniels) biopsy The clinical, and particularly the X ray picture, suggests that this method of obtaining positive nodes is not nearly comparable to histological confirmation by hilar glandular biopsies were the latter easily obtainable Since the introduc- [illegible] 1959 this has been accomplished [illegible] itive nodes in a considerable percentage of cases if the glands are palpable in the fossa supraclavicularis As a rule this already indicates extensive involvement of the lung and mediastinal glands Lofgren et al reported that in 89 per cent in a series of 194 cases of this type histologic diagnosis of sarcoidosis was established by Daniel s biopsy On the other hand, if the glands are not palpable the chances of getting histologic proof are markedly poorer in 47 cases only 32 per cent were histologically positive

In a series of 59 patients with sarcoidosis, Tarnowski reported 41 (70 per cent) positive on scalene node biopsy In the remaining part of his series histologic confirmation was obtained from other tissues It is noteworthy, however, that all 59 patients had clear roentgenologic evidence of mediastinal and pulmonary involvement.

There are several other reports on the value of scalene node biopsy in sarcoidosis and the incidence of positive findings varies widely This is quite natural and depends upon the extension of the sarcoid lesions if the process is still in the initial pulmonary stage, the likelihood of positive results is less than in widespread processes

There are already many reports upon the value of mediastinal biopsy obtained at mediastinoscopy Although Carlens does not cite any exact figures, he clearly emphasizes the value of mediastinal biopsies in confirming the diagnosis of sarcoidosis, and describes the abundant masses of glandular tissue seen and extracted during mediastinoscopy

Quite recently Lofgren et al reported on 35 cases in which there were no palpable glands in the supraclavicular fossa In these cases histologic confirmation was obtained in 91 per cent at mediastinoscopy, and these cases included 13 in which Daniel s biopsy had been negative

The present author has emphasized on several occasions the extraordinary features of mediastinal sarcoidosis which can be easily evaluated during mediastinoscopy Even macroscopically, clinical diagnosis of sarcoidosis has been easy in the acute or subacute group The mediastinal glands are generally abundant in number and large in size, bluish or violet in color and clearly distinguishable from the common antracotic glands The cut surface of the glands presents a slightly nodular picture it is grey or white and there is no black color as seen in other nonmalignant conditions

Another extreme seen on mediastinal examination is the chronic indurated form associated with intense scar tissue formation fixation and even shifting of tissues These glands are hard on touch blue or grey in color, black spots being encountered occasionally It is noteworthy, however that very often in chronic

cases the glands may show various stages of scar formation, some of them even resembling the fresh subacute form.

The material hitherto investigated consists of 28 cases of sarcoidosis, included in a series of 250 mediastinoscopies. Histologically positive results were obtained in 27 cases (96 per cent).

There is, however, some confusion at the present time as regards the histologic diagnosis, since tuberculosis is still quite common in Finland and pathologists are inclined to suspect tuberculosis more often than sarcoidosis even when signs of caseation are entirely missing Therefore, we have routinely performed inoculation of finely dispersed glandular tissue into guinea pigs in an effort to cause tuberculous lesions in these animals Hitherto, except in 1 case, all trials have been unsuccesful; nor has demonstration of tubercle bacilli in the sections been possible. On the basis of the clinical evidence, added to histologic data, all these cases have presented the characteristics of sarcoidosis

The film now to be shown first gives orientation as regards the mediastinal structures, and lesions due to other diseases, such as antracosis, metastactic carcinoma, thymoma or silicosis, are shown. Mediastinal sarcoidosis is presented in its acute proliferating form as well as in the extreme chronic form; intermediary stages can be seen in some patients. The mediastinal views are compared with the roentgen findings to illustrate the clinical stage of the pulmonary disease.

SUMMARY

Results are reported for 28 cases of mediastinal sarcoidosis included in a series of 250 mediastinoscopies. Mediastinal biopsies were positive in 96 per cent of the cases. The various macroscopic features of acute and chronic sarcoidosis are described. The mediastinoscopic procedure appears superior to other glandular biopsies for histologic confirmation of pulmonary sarcoidosis.

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EXFOLIATIVE CYTOLOGY IN OTOLARYNGOLOGY USING SULFHYDRYL ACTIVITY, ACRIDINE ORANGE AND MORPHOLOGIC STAINING PROCEDURES

By

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Abstract

Exfoliative cytology has been tested in a selected series of 50 cases of malignant tumours in the ENT area Wiping of the tumour surface with a cotton wool swab has proved the most suitable method of collecting samples To demonstrate cell morphology the May Grünwald Giemsa and Papanicolaou staining procedures have been used and found equally reliable The sulfhydryl (SH) activity was shown to be higher in malignant cells, which therefore can be recognized more easily and quickly than with morphological methods With fluorescence microscopy using acridine orange certain malignant cells are visualized by a bright red fluorescence The two cytochemical methods, and especially the SH technique, have proved a valuable complement to conventional staining procedures, but the final diagnosis must still depend on morphological criteria Our investigation has clearly demonstrated that cytodiagnosis can be of material value for a rapid diagnosis and is a suitable tool in oto rhino-laryngology

INTRODUCTION

Exfoliative cytology is the study of superficial cells and collections of cells which are continually shed off (exfoliated) from mucous membranes and the linings of the body cavities, and in particular from malignant tumours in such sites The methods is particularly suited to those regions of the body which are difficult to inspect and where the opportunities for biopsy are limited

MATERIAL AND COLLECTIONS OF SAMPLES

The study includes about 50 selected patients with tumours in the nose, para nasal sinuses, nasopharynx, oral cavity, pharynx, hypopharynx, oesophagus, larynx and external auditory meatus and middle ear In all cases the diagnosis has been verified by histopathological examination

The technique of collecting samples has varied on account of the different anatomy in the areas which have been examined Five methods have shown themselves suitable after testing

1 Direct wiping of the tumour surface with a cotton wool swab of varying length This technique is most suitable for visible lesions and has in practically all such cases given sufficient and representative material Collection of samples

cases the glands may show various stages of scar formation, some of them even resembling the fresh subacute form

The material hitherto investigated consists of 28 cases of sarcoidosis, included in a series of 250 mediastinoscopies Histologically positive results were obtained in 27 cases (96 per cent)

There is, however, some confusion at the present time as regards the histologic diagnosis, since tuberculosis is still quite common in Finland and pathologists are inclined to suspect tuberculosis more often than sarcoidosis even when signs of caseation are entirely missing Therefore, we have routinely performed inoculation of finely dispersed glandular tissue into guinea pigs in an effort to cause tuberculous lesions in these animals Hitherto, except in 1 case, all trials have been unsuccesful, nor has demonstration of tubercle bacilli in the sections been possible On the basis of the clinical evidence, added to histologic data, all these cases have presented the characteristics of sarcoidosis

The film now to be shown first gives orientation as regards the mediastinal structures, and lesions due to other diseases, such as antracosis, metastactic carcinoma, thymoma or silicosis, are shown Mediastinal sarcoidosis is presented in its acute proliferating form as well as in the extreme chronic form, intermediary stages can be seen in some patients The mediastinal views are compared with the roentgen findings to illustrate the clinical stage of the pulmonary disease

SUMMARY

Results are reported for 28 cases of mediastinal sarcoidosis included in a series of 250 mediastinoscopies Mediastinal biopsies were positive in 96 per cent of the cases The various macroscopic features of acute and chronic sarcoidosis are described The mediastinoscopic procedure appears superior to other glandular biopsies for histologic confirmation of pulmonary sarcoidosis

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Bahr's modification (1957) 2 2'-dihydroxy 6,6'-dinaphtyl-disulphide (DDD) reacts in excess at pH 8 5 with active SH groups in fixed tissue proteins with the formation of a colourless substance It can be converted to an intensely coloured azo compound by combination with diazotized 4-amino-3,6 dimethoxy-4'-nitro-azobenzene (Fast Black Salt or Echtschwarz salz K) The colourless oxidation product is insoluble in both water and ether alcohol, so that both the excess of DDD and other byproducts from the reaction can be washed from the tissue or smear with organic solvents *The result of the reaction is a deep blue colour of varying intensity, where the intensity is directly proportional to the number of accessible SH groups (Bahr, 1957, Bahr & Moeberger, 1958)*

After clinical and experimental testing on normal and malignant tissue Bahr & Moberger (1958) showed an increased concentration in the actively infiltrating parts of the tumour and in peripheral portions of solid cancer cords The superficial, SH rich, malignant cells are however very readily exfoliated and can, with cytological methods, be shown easily in various secretions of the body This was shown for the first time by Wiman (1959) Our intention in this study has been to determine if the same applies to malignant tumours within the E.N T. area

Fluorescence microscopy using acridine orange (AO)

The increased protein synthesis in malignant cells, among others, with increased concentration of desoxyribonucleic acid (DNA) in the cell nucleus and ribonucleic acid (RNA) in the cytoplasm and nucleolus is the basic cytochemical principle of the method described by von Bertalanffy & Bickis (1956) and von Bertalanffy, Masin & Masin (1958) This technique allows for differential staining of the two nuclei acids RNA in the cytoplasm and nucleolus gives a bright red fluorescence, DNA in the nuclear chromatin gives a green or yellow fluorescence In cytological cancer diagnosis the screening is made easier by the tumour cells' strong fluorescence, even if this is not specific for all forms of malignancy

May Grünwald Giemsa staining procedure (MGG)

The MGG staining gives some cytochemical informations proteins containing desoxyribonucleic acid (DNA) are stained purple-red, while ribonnucleic acid proteins (RNA) give a blue colour This fact can give some guidance in the diagnosis of cancer cells, which often have a higher proportion of RNA in cytoplasm and nucleolus compared, with other benign cells The most important advantage with the May Grunwald Giemsa method, however, is the clear and distinct morphology chiefly concerning the nucleus

Papanicolaou staining procedure

In exfoliative cytology this method has hitherto been the most frequently used, particularly for material from the female genital tract and the respiratory system. The Papanicolaou technique (1942) gives a beautiful polychromatic colour scale with good transparency The technique is widely known and does not require further description The preparations have been mounted in Canada Balsam

RESULTS

The Papanicolaou staining and the MGG staining which have been performed parallel in all cases have both given good preparations The latter has given distinct and well contrasted staining of chromatin structure and nucleolus, which is of decisive importance in diagnosis The varying staining properties and details of the cytoplasm are more clearly presented with Papanicolaous's technique We consider that the two staining methods compliment each other well

The method of acridine orange fluorescence microscopy is quick and simple to perform Undifferentiated tumour cells and adenocarcinoma cells have given a red fluorescence of their high RNA concentration, while cells from a differentiated keratinized squamous cell carcinoma have given an olive green appearance However, the method gives only preliminary diagnosis of malignancy Final diagnosis must rest on the basis of the morphology of the cells (Figs 8 and 16)

Our investigation has shown that the sulfhydryl activity is low in normal cells exfoliated from the mucous membrane of the upper respiratory tract Normal squamous epithelial cells cylindrical cells, goblet cells, leucocytes and erythrocytes seem like pale shadows The cancer cells, on the contrary, appear clear cut with clearly blue or violet coloured nuclei, cytoplasm and nucleoli showing the high sulfhydryl activity (Figs 3, 7, 15) This facilitates screening

DISCUSSION

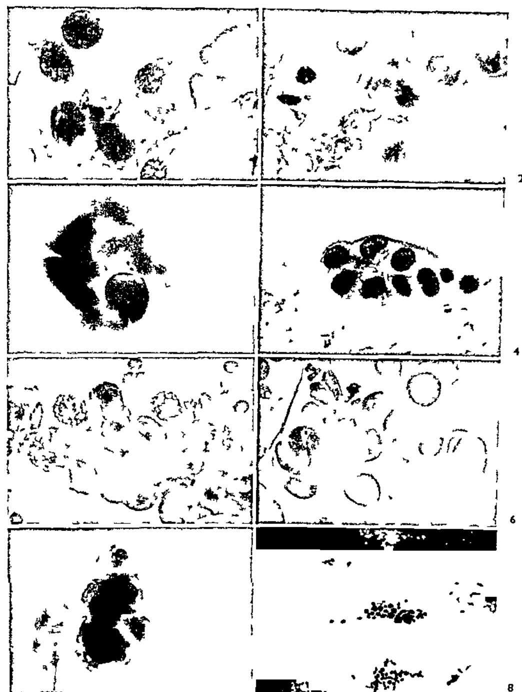
Our study confirms that cytodiagnosis is a justified method of examination in cases of tumours in the ear, nose and throat An essential advantage is that the method can give the correct diagnosis in less than one hour

Comparison between the morphological staining methods according to Papanicolaou and May Grunwald Giemsa has shown that both methods can be used with advantage in otorhinolaryngological cytological diagnosis The MGG staining has in our experience, given more detailed and better contrasted nuclear morphology, which is shown in Figs 1, 5, 9, 11, 13

We regard as an essential step forward in cytological diagnosis von Bertalanffy's acridine-orange-staining with fluorescence microscopy In this the abnormal protein synthesis which characterises malignant cells is used for special staining

The idea of replacing inaccurate and time consuming morphological methods with a simple cytochemical technique has been developed in the sulfhydryl method The increased sulfhydryl activity in malignant tumours has been known for a long time in cancer research In exfoliative cytology this fact has been used first by Wiman in lung cancer diagnosis (1959 1960, 1962) In our material malignant cells have been identified easily by their hyperchromasia and high concentration of protein bound sulfhydryl groups (Figs 3, 7, 15)

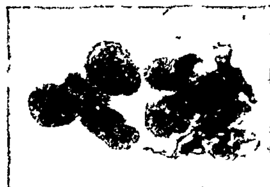
The effect of radiological treatment on mucous membranes and malignant tumours can be followed cytologically to a certain extent



Figs 1—16 Exfoliative Cytology in Otolaryngology Different staining methods showing malignant cells

Papanicolaou Figs 2 4 6 10 12 and 14
May—Grunwald—Giemsa Figs 1 5 9 11 and 13
Fluorochromation with acridine orange Figs. 8 and 16
Protein bound sulfhydryl groups (SH staining) Figs 3 7 and 15

9





11



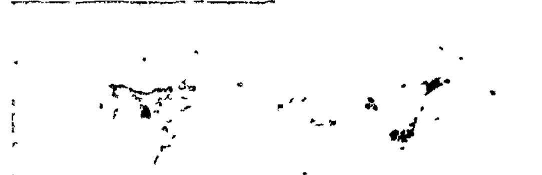


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THE TREATMENT OF PERITONSILLAR ABSCESS BY INCISION AND TONSILLECTOMY "A FROID' AT THE OTO LARYNGOLOGICAL HOSPITAL, UNIVERSITY OF HELSINKI

By

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From the Oto Laryngological Hospital, University of Helsinki

For several years it has been a custom at the Oto-Laryngological Hospital, University of Helsinki, to hospitalize patients with peritonsillar abscess The regular performance of tonsillectomy in these patients has met with success The acute and rather severe disease was rapidly cured upon this radical treatment and the patients got rid of their usually chronically infected tonsils Thus a permanent cure was achieved The investigations of Virtanen and Grahne showed the results of this form of therapy to be promising on the average, they did not observe any severer complications

Thus the treatment of peritonsillar abscess would have been a finally and unquestionably settled question if there were not several factors to call for a new analysis of this mode of therapy

It is well known that the tonsillectomy "a chaud" performed in local anaesthesia in the acute phase of peritonsillar abscess is usually a much greater strain for the acutely ill patient than the operation "a froid' during the silent phase of the illness Furthermore, the tonsillectomy "a froid" is technically somewhat easier because there is no trismus If the operation is to be performed in the acute phase it should be done in general anaesthesia As yet, however, we have very limited resources in this regard This is particularly true about duty time Furthermore, tonsillectomy "a chaud" in the acute phase of peritonsillar abscess frequently must be performed by the otologist on duty at night thus substantially increasing his burden and that of the personnel of the surgical ward This means greatly prolonged waiting for the other emergency cases and increased hospital expenses to cover the costs of out of-hours work

In view of these facts other forms of therapy must be considered

MATERIAL AND METHODS

To establish the *pro* and *con* of tonsillectomy "a froid" we studied the patients with peritonsillar abscess treated in 1961 at the wards and the out patient department of the Oto-Laryngological Hospital, University of Helsinki The series comprises 308 patients, of which 63 patients were treated in the acute phase of the disease at the wards and 245 patients at the out patient department

The tonsillectomy "a froid' has been employed at this hospital since 1958 The abscess was incidised and the patient was treated with peroral penicillin The

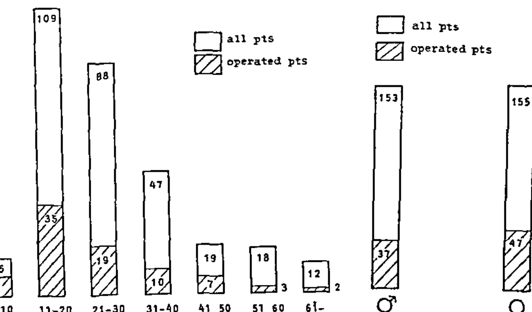


Fig 1

Fig 2

tonsillectomy was postponed to be included in the ordinary operation program of the next few days or it was suspended to a later "cold" phase We usually have avoided to perform tonsillectomy in the "tepid" phase of the disease

RESULTS

The distribution of the series by age and sex is seen in Figs 1 and 2 The distribution by sex is even, the number of patients is greatest in the age groups 10—20 and 20—30 years

About 60 per cent of the patients, 184 cases in all, had earlier anamnestic fits of tonsillitis Of these, 116 patients earlier had only tonsillitis, 41 patients had tonsillitis and peritonsillar abscess in the past and 27 patients had only had an abscess In the last number, the abscess inducing tonsillitis is not considered Thus, 68 patients in all had earlier had an abscess

Tonsillectomy was performed immediately upon hospitalization in only 5 cases, i e in 1 6 per cent of the series — 79 patients (25 6 per cent) underwent tonsillectomy in a later phase The total of operated patients thus only amounted to some 27 2 per cent In the past, practically all patients with peritonsillar abscess were operated upon — the new system enabled a reduction of the frequence of tonsillectomy by nearly three fourths

The frequence of anamnestic tonsillitis in the series is shown in Fig 3, which also shows the relationship between anamnestic tonsillitis and later tonsillectomy The patients with anamnestic tonsillitis seem to have had a greater interest in surgical treatment

What then has the late prognosis of these 308 patients been like? It was evident

that all of them were cured of the peritonsillar abscess and there were no complications worth mentioning The follow-up investigation revealed that 22 non-operated patients (7 1 per cent) developed a new peritonsillar abscess within the short follow up period

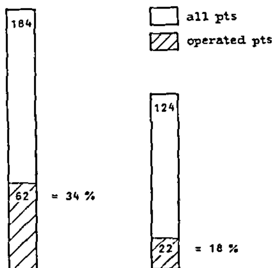


Fig 3

DISCUSSION

The purpose of this investigation was to evaluate the profits and the eventual drawbacks of the postponement of tonsillectomy to a later "cold" phase of the disease As a result of the analysis of these 308 patients we have arrived upon the following conclusions

1) The recovery of the incised patients as to the acute phase of the disease has been comparable to the recovery of the tonsillectomized patients A good draining of the abscess is, however, a prerequisite for rapid recovery If this was not feasible tonsillectomy was performed There were no severer postoperative hemorrhages

2) The operations, usually performed in local anaesthesia, were less painful and straining for the patient than tonsillectomy "a chaud".

3) Incision only enables work- and time saving out patient care of 80 per cent of the patients The otologist and the personnel at duty can be spared and the costs reduced

4) The main drawback of tonsillectomy "a froid" is that is left undone in about three out of four patients They keep their often quite inflamed tonsils for years with frequent recidivation The number of negligent patients certainly can be reduced by a more rigorous and adequate explaining to the patient of the importance of tonsillectomy in the near future

The consideration of other possible drawbacks of the infected tonsils left in the patient to 'cool down' is irrelevant to the problem investigated

SUMMARY

A series of 308 patients with peritonsillar abscess treated with incision and tonsillectomy ' a froid ' at the wards and the out patient department at the Oto-Laryngological Hospital, University of Helsinki, is represented The series com prises all the cases of peritonsillar abscess diagnosed at the hospital in 1961 The age and sex distributions of the series are even Some 60 per cent of the patients proved to have had an anamnestic fit of tonsillitis in the past. The mode of treatment described by the authors proved to be as effective but by far less cumbersome than the earlier method of tonsillectomy "a chaud ' There were no noteworthy complications It was possible to treat some 80 per cent of the patients at the out patient department by incision — however, only one out of four patients returned for tonsillectomy "a froid In the other cases, a follow-up examination showed recidivation to be quite frequent

THE ADVANTAGES OF BINAURAL HEARING FOR THE UNDERSTANDING OF SPEECH

By

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Goteborg

The effect of binaural as compared with monaural listening on the intelligibility of speech was studied with the aid of an artificial head Speech signals reaching the head at various azimuths were recorded by means of condenser microphones in the head at the position of the eardrums The recorded signals were then analyzed with the sound spectrograph to compare the intensity and frequency distribution of the speech sounds reaching the two ears PB lists of Swedish monosyllables were recorded via the two microphones simultaneously at various azimuths The recordings were played back via binaural headphones to a group of listeners and their intelligibility was measured The intelligibility for binaural listening was found to be significantly better than for monaural, even when the speech, reaching the ear turned away from the sound source had a very low "information content" according to the spectrographic analysis, and was almost unintelligible when heard monaurally The results are discussed in relation to stereophonic hearing aids and the handicaps of hearing loss

THE TENSOR TYMPANI REFLEX IN OPERATIVE TREATMENT OF TRIGEMINAL NEURALGIA

By

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The trigeminal nerve is a mixed nerve The larger portion is called portio major and is sensible, the smaller portion, portio minor, is motor and innervates via n mandibularis amongst others the chewing musculature, m tensor veli palatini and m tensor tympani

In injury to the motor portion of the trigeminal nerve through trauma, in the form of haemorrhage or fracture, destruction by tumorous growth or by severance in connection with operation for trigeminal neuralgia, paralysis of the chewing musculature occurs It is accompanied by more or less pronounced deviation of the jaw on the affected side, and loss of function in m tensor veli palatini and m tensor tympani Conversely one can say, that functional loss in either of these muscles can give information on the functional condition of the trigeminal motor branch A manifest deviation of the jaw is easy to establish when it is pronounced, but determination becomes uncertain in slighter cases Paralysis of m tensor veli palatini is accompanied by a reduced ability to actively open the Eustachian tube when swallowing and as a result thereof an otosalpingitis can quickly develop In certain cases, however, the tubal occlusion disappears and the tube remains open, whereby the symptoms disappear The loss of the tensor tympani reflex can, under certain conditions, be utilised for the determination of the trigeminal motor function The reflex can be activated by giving an air puff against the orbital region (Klockhoff and Andersson 1960) The reflex activity can be shown and registered with the help of acoustic impedance measurement technique (Metz 1946, Andersson, Holmgren & Holst 1956, Terkildsen & Scott Nielsen 1960, Klockhoff 1961) Absence of the tensor tympani reflex points to injury in the motor branch, provided that no other obstacle to the release of the reflex in the form of conduction loss can be shown in the middle ear and this is investigated with the help of the stapedius reflex test. If the latter reflex can be elicited by acoustic or electric stimulation it indicates that the middle ear is normal The audiological criteria for injury of the motor portion of the trigeminal nerve, consequently amounts to the absence of the tensor reflex with a stapedius reflex by acoustic stimulation

In the ear clinic of Sahlgrenska Sjukhuset, Goteborg, we have since 1961 registered all patients with trigeminal neuralgia, who have been remitted from the neuro-surgical clinic for pre- and postoperative examination

These have comprised E N T and oto-neurological status, tone audiometry and determination of stapedius and tensor tympani reflexes.

The operative treatment of trigeminal neuralgias which was here, has been partial severance of portio major immediately proximal to the gasserian ganglion

In one of the cases examined, the neuro surgeon had to intentionally sever the motor portion also examination of this patient showed that neither the tensor tympani- nor the stapedius reflexes could be stimulated by means of air-puffs, while on the contrary, the stapedius reflex could be obtained by acoustic stimulation

RESULTS

34 patients with trigeminal neuralgia have been examined both pre and post-operatively, together with 6 cases, who had been operated upon earlier, the latter only post-operatively The final determination of the tensor muscles' function was made after three months It is important to let the post-operative reaction wear off During the first months after operation, there were, for a period of about 2—3 weeks, also signs of otosalpingitis in 4 cases and hemato tympanon in 5 cases All these 9 cases had both negative tensor- and stapedius reflex In the final determination, it was seen that 11 of the 40 cases lacked the tensor tympani reflex while the stapedius reflex was normal and there was a clear jaw deviation, a sign of damage to the trigeminal motor branch In the other 29 cases, the tensor- as well as the stapedius reflexes could be normally demonstrated See Table I

In all 40 cases there was post operative reduction of the pain threshold of trigeminal neuralgia

Table I *Postoperative results*

Reflexes	After one week				After three months			
	Hemato tymp	Oto salp	Norm middl ear	Total	Hemato tymp	Oto salp	Norm m ddl ear	Total
Tens tymp neg	5	4	16	25	0	0	11	11
» » pos	0	0	15	15	0	0	29	29
Stapedius neg	5	4	0	9	0	0	0	0
» » pos	0	0	31	31	0	0	40	40

DISCUSSION

The determination of the tensor tympani reflex does not appear to have been used previously as a clinical method for testing trigeminal motor function, in connection with operation for trigeminal neuralgia Jepsen (1955) as well as Klockhoff (1961), have examined cases of trigeminal paralysis, in order to show that the response in acoustic stimulation could only come from m stapedius

The physiological release mechanism for the m tensor tympani reflex is still being debated According to Terkildsen (1962) and Holst et al (1963) the tensor tympani reflex can be released by strong sound stimuli, which Klockhoff (1961) on the contrary, denies

The last mentioned author makes use of air puffs against the orbital region as stimuli, whereby the tensor tympani reflex is released as a partial phenomenon in a "startle response" Klockhoff (1961) considers that he also has been able to show, that the stapedius reflex is released simultaneously with the tensor reflex by an air puff against the eye Lidén and Nordlund (1961) have visually verified this in the exploration of the muscles of the middle ear The stapedius contraction gives here an even greater reflex movement than with acoustic stimulation (100 dB, 1000 Hz)

Under normal conditions, using air puffs, both tensor tympani as well as stapedius reflexes are obtained The afferent portion of the stapedius reflex, according to Pearson (1949), goes via n facialis and the tensor reflex via n trigeminus The efferent portion to the tensor muscle goes via the motor part of n trigeminus

In spite of cutting the sensory portion of the trigeminal nerve, one can never theless, obtain the tensor reflex in most of our cases One would think that the reflex arc is now completely broken, but the following explains why this is not the case

One knows that proprioceptive fibres are certainly present in portio minor of the trigeminal nerve, especially from the outer eye and chewing musculature's muscle spindles (Pearson 1949 and others) With air-puffs against the orbital region the patient cannot help wincing or screwing up the eyes and just these movements activate the muscle spindles from whence impulses pass in the proprioceptive fibres up to nucleus trigemini mesencephalicus in the mesencephalon This nucleus is in intimate contact with both trigeminus- and facialis' motor nuclei Consequently, through a switchover in this region, an air puff against the orbital region can give rise to an impulse which via these fibres, gives a contraction of the tensor tympani and stapedius muscles The reflex accordingly goes in the motor portion of trigeminus to the mesencephalic nucleus and severance of the sensory nerve has not broken the reflex route See Fig 1

On the contrary, where the stapedius muscle is concerned, it implies damage

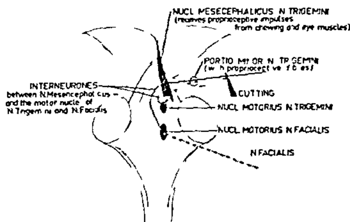


Fig 1 The mesencephalic region with the reflex arcs

to the proprioceptive course of trigeminus in portio minor. Since by *acoustic* stimulation in all these 11 cases, one could release a normal stapedius reflex.

This also constitutes a criterion that the middle ear was normal and did not impede the release of the tensor reflex

As a further sign of trigeminal motor injury, there was also obvious jaw deviation in all the 11 cases

Thereby the criteria of trigeminal motor damage were fulfilled.

ZUSAMMENFASSUNG

Um etwaige Schaden am motorischen Teil des Nervus Trigeminus bei Operation des Nervens bei Trigeminus-Neuralgie festzustellen, wurde der Tensor Tympani Reflex nach Klockhoff und Andersson angewandt Das Fehlen des Tensorreflexes, den man vor der Operation bemerken konnte, betrachtete man als Anzeichen fur einen solchen Schaden unter Voraussetzung, dass der Stapediusreflex weiterhin ausgelost werden konnte Verletzung des motorischen Teils konnte in 11 von 40 operierten Fallen mit Trigeminus-neuralgie festgestellt werden Man konnte auch gut Übereinstimmung mit anderen Anzeichen bei Trigeminuslahmung beobachten, wie z B Unterkieferabweichungen

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SIGNIFICANCE OF THE STAPEDIUS REFLEX FOR THE UNDERSTANDING OF SPEECH

By

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The activity of the intra aural muscles has been extensively investigated in recent years, but their physiological significance is still not entirely clear Reflex contractions of the muscles are readily elicited in response to sounds of sufficient intensity Since these contractions can easily be shown to reduce the transmission of sound to the inner ear, especially that of the lower frequencies (H C Wiggers, 1937, Wever and Bray, 1942), they have generally been interpreted as protecting the organ of Corti against excessive stimulation, much as the pupillary reflex protects the retina against over intense light Such a protective action has been demonstrated both in animals and in man (Galambos and Rupert, 1959, Fletcher and Riopelle, 1960, D Hilding, 1961)

This protective action, afforded particularly by the stapedius muscle is pro bably of some benefit to man in the noisy conditions of present day living, even though recent studies (Glorig and Nixon, 1962, Rosen et al, 1962) seem to indicate that only those dwelling in surroundings not reached by the sounds of civilization are safe from a gradually cumulative acoustic trauma that occurs in spite of the stapedius reflex Furthermore, from an evolutionary point of view it is difficult to understand how the intra aural muscles and their reflexes could have developed if their function were only that of protecting the inner ear against acoustic insult Since sounds of sufficient intensity to injure the cochlear hair cells rarely occur in nature, such protection could have little survival value for either animals or man The pupillary reflex furnishes a less apt comparison than would at first appear

The protection actually conferred by the stapedius reflex is at best limited Although the latency of contraction is only about 10 msec, maximum tension may not be reached for 100 msec or more (R Wersall 1958) Sudden, intense sounds may therefore injure the inner ear before this protective mechanism can become effective Nor is the full tension maintained in response to continued stimulation Instead, the tension drops to about 50 % of its maximum value after a few seconds, as a result of 'adaptation' The effect of contraction is to increase the stiffness of the ossicular chain, shifting its characteristic frequency upwards, so that the transmission of sounds below 1000 cps is reduced especially that of the lowest frequencies Against frequencies above 1000 cps the contract

ions are almost entirely ineffective, although it is these higher frequencies that are most likely to injure the organ of Corti

A different interpretation of the intra aural reflexes was suggested by Stevens and Davis (1938), based on the fact that low frequency tones easily mask high frequencies, but not vice-versa Selective reduction in the transmission of low-frequency tones to the inner ear must reduce their masking effect and improve the hearing of tones of higher frequency Such a shift in the transmission characteristic of the middle ear should obviously be of considerable value to man by helping him to hear, in the presence of low frequency background noise, the speech frequencies above 1000 cps, which carry much more information than those below 1000 cps It should also be of survival value to animals, making it easier for them to hear faint sounds made by their prey or by their enemies, in spite of other noises around them or the physiological noises in their own heads According to this interpretation, the physiological role of the stapedius reflex is to improve the information to-noise ratio by a high pass filtering action Although such a possibility is mentioned by Perlman (1960), it has been largely neglected by other authors The problem is of great importance for stapes sugery, and especially in stapedectomy, which usually involves removal of the stapedius tendon with the ossicle

The result of the operation is usually measured by means of pure tone and speech audiograms, both carried out in quiet surroundings In reality it is often the ability to understand speech in noisy environments that is most important for patients, but the surgeon seldom takes that need into account It is not unusual for a patient to report a few weeks after stapedectomy "When everything is quiet I can hear a pin drop, but when it is noisy I can hardly understand what people say" Low frequency noise disturbs such patients very much, and some find traffic noises so unpleasant that at first they refuse to venture out on the street This difficulty gradually diminishes, but whether it is because the patient becomes accustomed to the noise, or whether his ability to understand speech in the presence of noise improves, is still not clear

The aim of the present investigation has been to determine, first, whether the patient's immediate difficulty during the first month can be demonstrated by means of discrimination tests in noise, and second, whether the results is altered when the operative procedure is modified

METHOD

The hearing was tested before and after operation with the usual tone-and speech audiometry and with a discrimination test in noise For the latter test, lists of monosyllabic Swedish words (Liden, 1954) were delivered to the ear by a headphone The background noise consisted of low-pass filtered white noise with a cut-off frequency of about 500 cps When the speech and noise intensities were equal, the intelligibility scores averaged about 40% Each test consisted of 25 words In the preoperative tests the intensity was set at the comfort level, and in the postoperative tests about 10 db below the level of discomfort Postoperative measurements were made one month after stapedectomy

Table I *Speech discrimination in noise and hearing level in quiet before and after stapedectomy*

	Number	Discrimination in noise		Averge gain in hearing level in quiet	
		Worse	Same or better	With discrim. worse	With discrim. same or better
Stapedectomies	31	17 (55 %)	14 (45 %)	32 db	32 db
Tendon removed	20	13 (65 %)	7 (35 %)	30 db	30 db
Tendon preserved	11	4 (36 %)	7 (64 %)	40 db	35 db

MATERIAL

Hearing tests in quiet and in noise were performed on 31 otosclerotic patients before and after operation, and on 36 patients after operation only In the latter cases the hearing of the operated ear was compared with that of the unoperated ear The patients included in the study had all undergone stapedectomy, either with removal of the tendon according to Schuknecht et al (1960), or with preservation of the tendon according to Herberts (1963)

RESULTS

The results are presented in Tables I and II If the discrimination score in noise for the operated ear was 10 % lower after operation than before (Table I), or 10 % lower than for the unoperated ear (Table II), the result was classified as *worse* Typical scores for discrimination tests before and after operation were for example, 56 % before and 36 % after, or 60 % before and 28 % after

Of 20 stapedectomies with the tendon removed, 13 or 65 % showed a significantly worse discrimination in noise after operation, whereas of 11 cases with the tendon preserved, only 4 (36 %) had worse discrimination after operation When the postoperative discrimination scores in noise for the operated ear are compared with those for the unoperated ear, it is seen that in 70 % of the patients the understanding of speech in noise is worse with the operated ear

Table II *Speech discrimination in noise and hearing level in quiet*

Comparison between operated and non-operated ears

	Number	Postop discrimination in noise	Average hearing level in quiet			
		Op ear worse than non op	Op ear worse		Op ear same or better	
			Op	Non op	Op	Non op
Stapedectomies	36	25 (70 %)	24	39	17	30
Tendon removed	21	16 (76 %)	24	35	19	26
Tendon preserved	15	9 (60 %)	24	45	17	30

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		Op ear worse than non op	Op ear worse		Op ear same or better	
			Op	Non op	Op	Non op
Stapedectomies	36	25 (70 %)	24	3[illegible]	17	30
Tendon removed	21	16 (76 %)	24	35	19	2[illegible]
Tendon preserved	15	9 (60 %)	24	45	17	30

than with the unoperated in spite of the fact that the thresholds for the operated ear have been restored to normal In no case was there any indication that the operation produced any cochlear loss

DISCUSSION

From this investigation it is clear that for a full evaluation of hearing in connection with stapes operations tests beyond simple tone and speech audiometry are required A complete closure of the gap between the air and bone conduction threshold curves together with normal inner ear function does not necessarily mean normal hearing Speech discrimination tests in noise should be a useful addition to the usual audiometry for evaluating the results of operations for the improvement of hearing This study has shown that stapedectomized patients have poorer discrimination in noise than normal hearing persons The results suggest that the stapedius tendon should be preserved whenever possible since the muscle seems to be important for the understanding of speech in noise

Patients complain immediately after operation that they hear too much , are sensitive to loud sounds and have difficulty in understanding After a few months their trouble decreases Further investigations will show whether in spite of the subjective improvement their discrimination in noise remains poor Perlman (1962) mentions one type of patient that he has encountered with persistent intolerance to loud sounds after operation These patients also had reduced discrimination scores but their audiograms revealed sensory loss which was perhaps worse after operation than before and recruitment probably enhanced the discomfort produced by loud noises In none of our cases was there any indication that the operation produced any sensory loss with reduced discrimination of speech in quiet surroundings as a result

The phenomenon of contralateral remote masking defined by Ward (1961) as the elevation of threshold sensitivity to a low frequency tone in one ear produced by a high frequency band of noise in the other is attributed by him to reflex activation of the stapedius muscle an inference entirely in accord with our view that a major function of the stapedius is to act as a high pass filter Simmons and Beatty (1962) suggest that the amplitude modulations produced by the contractions of the stapedius may aid in auditory analysis or help to maintain attention Our findings do not exclude such an interpretation of the physiological role of the muscle but they strongly support the hypothesis that its contractions favor the hearing of the higher frequencis by reducing the transmission of the lower frequencies to the cochlea and thus improve the information to-noise ratio

CONCLUSIONS

1 An important function of the stapedius muscle appears to be that of improving the information to-noise ratio at the oval window by acting as a high pass filter

2 In the various types of stapes operations the stapedius tendon should be preserved insofar as possible

ZUSAMMENFASSUNG

Nach allgemeiner Auffassung ist die Hauptfunktion des Stapediusreflexes das Innenohr vor starken Tonen und Gerauschen zu schutzen Ein anderer Effekt des Reflexes welcher weniger bekannt jedoch wichtig sowohl fur Tiere als auch fur Menschen ist besteht darin dass die Kontraktion des M Stapedius die niederen Frequenzen zuruckhalt die sonst die hoheren Frequenzen maskieren Die Funktion des Reflexes kann also mit der eines Hochpassfilters verglichen werden wodurch das Horen der hohen Frequenzen mit ihrem grosseren Informationsinhalt relativ verbessert wird

Studien von Patienten mit nicht funktionierendem Stapediusmuskel nach Stapesectomi zeigten trotz normaler Schwellenwerte ein herabgesetztes Vermogen, Sprache in Larm zu verstehen welches diese Hypothese bekraftigt

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EXPERIMENTAL STUDIES ON SOUND TRANSMISSION IN THE HUMAN EAR[1]

III

INFLUENCE OF THE STAPEDIUS AND TENSOR TYMPANI MUSCLES

By

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Abstract

An experimental set up in which an automatic sound level recorder is employed has been used to obtain a graphic representation of the sound conduction in specimens of human temporal bones The influence of application of various forces to the stapedius and tensor tympani muscles has been investigated with special respect to output to input ratio and the formation of harmonics

When the human ear is exposed to sound of high intensity the mechanism transferring the vibrations to the cochlea will be different from that which conveys the sound at low intensity

The following aspects of the influence of the tympanic muscles on sound transmission were studied in the present investigation

1 The changes in the transmission of sound caused by pull applied to the muscles separately and both together

2 The phase shift of the transferred sound signal produced by pull applied to the muscles

3 The effect of the muscles upon the formation of harmonics at high sound levels

A number of measurements of the transmission of sound in specimens of the human temporal bone have been performed.

In the experimental set up, which has been described in a previous paper (1963) a well defined pure tone — the input signal — is applied to the external meatus After passage through the conduction system of the middle ear and the cochlea the sound is measured by a microphone as vibrations of the round window Comparison of this output signal with the input signal yields (1) the numerical value of the transmission, i e the ratio of output to input, (2) the relative phase of the output signal and (3) the harmonics which may be formed in the process of transmission

In the temporal bone the stapedius and tensor muscles were connected to gauges calibrated in grammes These gauges were used for the simple application of known axial force to the two muscles.

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[1] Aided by grants from the Danish State Research Foundation Philips Fond and Oticon Fond.

The transmission of sound was measured (1) without application of external forces to the muscles the normal condition, and (2) with various forces applied to the two muscles Fig 1 shows the effect of 10 g applied to the stapedius and (below) 50 g applied to the tensor tympani The pronounced difference is further illustrated in Fig 2 showing the effects at 500 c/s and 3000 c/s for various applied forces

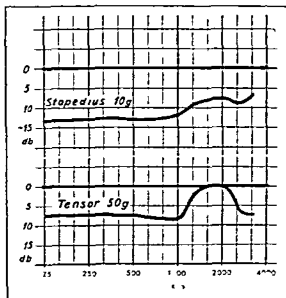


Fig 1 The attenuation caused by application of external forces as indicated to the stapedius and tensor tympani muscles The reference (0 db) corresponds to the normal condition.

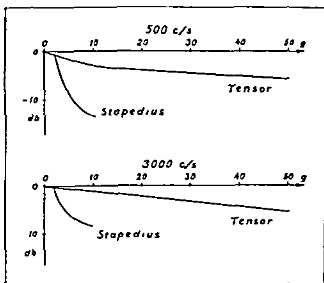


Fig 2. The attenuation at 500 c/s (above) and 3000 c/s as a function of the force applied separately to the stapedius and to the tensor tympani.

The function of the stapedius and tensor muscles might well be interdependent, which entails that the combined action of the two muscles would be different from the addition of the effects of the two muscles separately The action of one muscle might for example reduce the effect of the other

In order to clarify this problem, measurements were performed throughout the frequency spectrum 125—3500 c/s for several combinations of load on the two muscles To illustrate these studies, two characteristic sets of curves for the attenuation of transmission produced by combined loads are shown in Fig 3 Only the highest forces in combination result in a moderate deviation from the complete independence of the action of the two muscles upon the attenuation of transmission

Further information concerning the mechanisms involved in the muscular action may be obtained from measurement of the phase shifts in the output signal caused by the application of forces to the two muscles Fig 4 shows that pull applied to stapedius produced a phase shift the sign of which was the same as that caused by a general increase in stiffness The effect is pronounced at the higher frequencies and decreases to about zero at the lowest frequencies, though the attenuation of the transmitted signal is most pronounced for low frequencies A comparison of this with our previously published results (1963) shows that there is a definite resemblance between a pull applied to the stapedius and negative air pressure in the tympanic cavity both regarding the attenuation and phase shift

In contrast to this, a pull applied to the tensor tympani has little effect on the phase of a transmitted signal, and its action may consequently be regarded

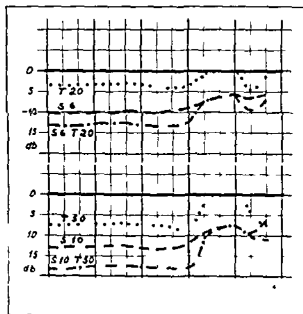


Fig 3 The attenuation caused by pull externally applied to the stapedius and tensor tympani muscles separately and for the combined application of pull to both muscles S 6 6 g force applied to the stapedius etc

fairly similar to that of an increased friction. The simultaneous application of pull to both muscles appears to cause much the same phase shifts as would result from adding the two separate effects.

For purely physical reasons there will be changes in the transmission of high intensity signals through any transmission system as the limit of energy transferring capacity is approached. If the input signal to, e. g., a loudspeaker system is gradually increased, it will at a certain level be experienced that the output does not follow the increase in input. It is not possible to transmit arbitrarily large signals and this limitation is extremely useful, for example some of the noise peaks from a wireless would otherwise easily destroy our hearing. As the limitation in the quantity of the transmitted sound from a loudspeaker sets in the listener will notice a change in the quality of the sound: it now becomes distorted and a corresponding amount of harmonics will be present.

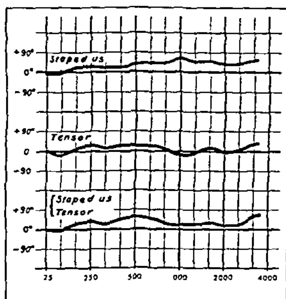


Fig. 4. The phase of the output signal: external pull applied to the stapedius muscle (upper), the tensor tympani muscle (middle) and to both muscles simultaneously (lower) relative to the phase of the output signal in the normal condition. Positive phase angle corresponds to "increased stiffness".

Measurements on the temporal bone of the second and third harmonics at input intensities amounting to 127 db above 2 · 10^{-4} dyne/cm² show that the intensity of these harmonics in the output signal does not exceed a level 20 db lower than the fundamental. This has been measured without external forces applied to the two muscles as well as with pull applied to both muscles separately and simultaneously. However, it would not be correct to conclude from the low distortion that the limiting mechanisms of purely physical nature is not in action.

When the output signal is recorded throughout the range 125—3500 c/s at

input sound pressure levels stepwise increased by 10 db, a group of curves as shown in Fig. 5 may be obtained. (For ease of survey the output signal corresponding to a moderate input sound pressure level: 97 db above $2 \cdot 10^{-4}$ dyne/cm² has been taken as reference, 0 db.) The output signal does not increase corresponding to the increase in input signal: there is no longer proportionality between output and input. At these high sound levels there is non-proportionality — or usually termed: nonlinearity. An input sound pressure of 137 db above $2 \cdot 10^{-4}$ dyne/cm² results in an output signal which above 1000 c/s is about 10 db less than corresponding to the transmission at moderate signal levels. This demonstrates a rather efficient limiting mechanism at the higher frequencies.

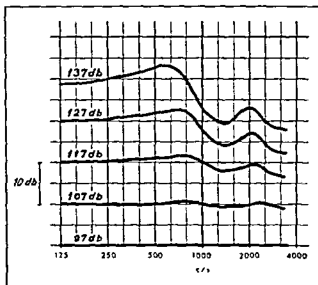


Fig 5. The output signal at input sound pressure levels 97, 107, 117, 127 and 137 db above $2 \cdot 10^{-4}$dyne/cm². The output signal at 98 db input sound pressure is used as reference

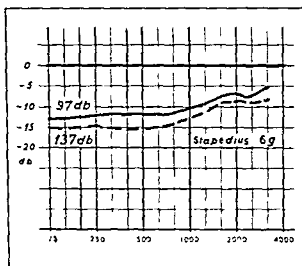


Fig 6 The attenuation caused by a pull (6 g) applied to the stapedius muscle at 97 db and at 137 db input sound pressure level

The attenuating effect of the stapedius and tensor tympani muscles at these high intensities has also been examined Fig 6 shows the attenuation caused by a force of 6 g applied to the stapedius at a moderate and at a high sound level The attenuating action of the muscle is further increased at the high sound level As to the low frequencies the same is true for the function of tensor tympani (Fig 7) The simultaneous application of forces to both muscles (Fig 8) causes an attenuation which is practically equal to the sum of two attenuations obtained by separate action

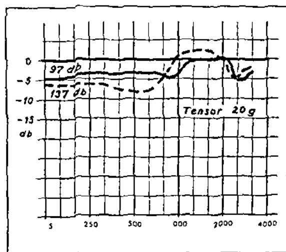


Fig 7 The attenuation caused by a pull (20 g) applied to the tensor tympani muscle at 97 db and at 137 db input sound pressure level

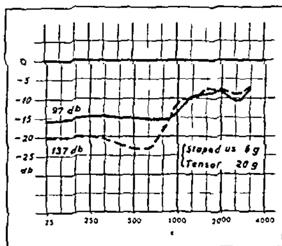


Fig 8 The attenuation caused by pull applied simultaneously to the staped us (6 g) and the tensor tympani (20 g) at input sound pressure levels 97 db and 137 db

CONCLUSIONS

A In the sound conduction system of the examined temporal bone three attenuating mechanisms have been demonstrated

√ 1) Pull applied to the stapedius muscle causes attenuation at all frequencies measured, but most pronounced in the low frequency range

✓ 2) Pull applied to the tensor tympani also causes attenuation of the low frequency range, but the effect is definitely smaller than that of the stapedius

3) At high input sound pressures an independent physical mechanism tends to limit the transmission of the higher frequencies

B The three mechanisms essentially act without formation of harmonics

C The action of the two muscles upon the transmission of sound appears to be independent

D The total attenuation of the three mechanisms amounts to about 20 db throughout the frequency range 125—3500 c/s at an input sound pressure of 137 db above 2 10^{-4} dyne/cm^2

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MIDDLE EAR MUSCLE REFLEXES ELICITED BY ACOUSTIC AND NONACOUSTIC STIMULATION

By

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Abstract

The function of the tensor tympani muscle has been studied by direct observation of its tendon Results of this study together with a survey of the middle ear muscle reflexes in man are reported

Contractions of the tympanic muscles can be easily inspected and recorded during experimental investigations in animals

In human subjects, however, this is much more difficult

The stapedius tendon can be inspected through perforated ear drums and during operative procedures Owing to the anatomical conditions, the tensor tendon has previously been considered inaccessible to inspection As a result, we know very little about the tensor tympani muscle and its function in humans (Jepsen, 1955, Klockhoff, 1961)

Three years ago we were able to demonstrate (at Namdal Hospital, Namsos, Norway) that the tensor tendon could be studied during most operations for otosclerosis (Djupesland, 1962) During 125 operations performed by Professor O Opheim (Rikshospitalet, Oslo, Norway) this study could be carried out in all but 11 cases

I will describe briefly some of the data obtained by recording of impedance and direct inspection of the tendons of the intra aural muscles

Recording contraction of the tensor tympani muscle has been possible, using a mechano-electronic transducer (RCA 5734), attached to a horseshoe-shaped metal head band fixed to the cranial periosteum by three sharp steel prongs (Fig 1) A small hook is attached to the tensor tendon and the changes in tension are transmitted by a thread to the mechano-electronic transducer

Activity in the stapedius and the tensor tympani muscle has also been recorded electromyographically during operations for otosclerosis

A simple, sensitive and stable apparatus is required to record the changes in acoustic impedance of the ear drum The following modification of Terkildsen and Scott Nielsen's impedance meter was employed (Fig 2)

The head band and accompanying metal rod for the aural canal were removed The transducer block is suspended from a movable and easily regulated arm Two short rubber tubes are attached to the transducer block, one with a side tube for adjusting and measuring the ear canal pressure Two narrow polyethy

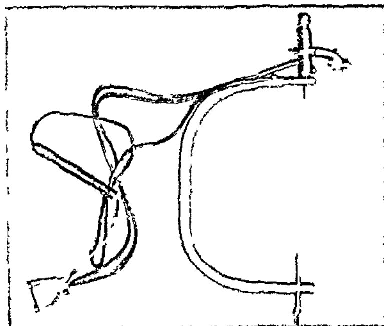


Fig 1 Horseshoe shaped metal head band with three sharp steel prongs which are screwed to the patient's skull The mechano-electronic transducer is attached to the head band by an adjustable arm

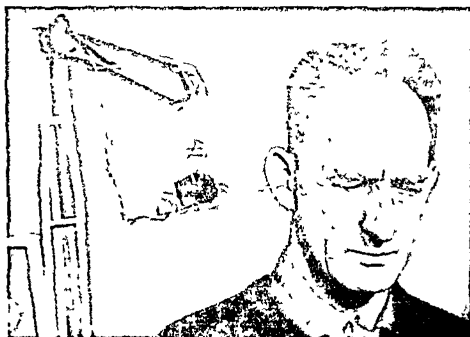


Fig 2 Modification of Terkildsen and Scott Nielsen's impedance meter Description, see the text.

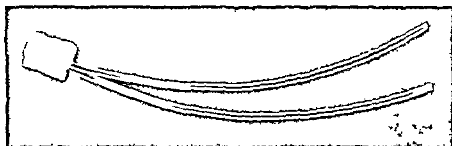


Fig 3 Rubber stopper with attached polyethylene tubes

lene tubes are pushed through a soft rubber stopper (Fig 3) Stoppers of different sizes and shapes are made, to fit all types of aural canals They can be washed and reused

The rubber stopper is introduced as far as possible into the ear canal, using forceps The less the space between the stopper and the ear drum, the more sensitive is the apparatus to alterations in the impedance of the eardrum The other ends of the two polyethylene tubes are led into two rubber tubes attached *firmly to the transducer-block*

This arrangement is very stable The patient can move his head considerably without throwing the recording system out of balance The investigation causes a minimum of discomfort Recumbent patients can be examined easily

Working on non anesthetized rabbits impedance changes have been recorded on sound stimulation of the contralateral ear of 400—40 000 cps and possibly even higher Following experimental stapedius paralysis, practically the same impedance threshold is obtained at all frequencies This demonstrates that interplay of the tympanic muscles is not necessary for the production of impedance changes on acoustic stimulation, as has been suggested by Terkildsen (1962)

Upon investigating 55 persons with normal ear drum and normal hearing for the age, a spontaneous change in the impedance of the ear drum in some of them was found Spontaneous impedance changes are most prominent in nervous and tense *individuals and are related to general motor activity When the subjects* relax, the spontaneous changes decrease and can even disappear

Contractions of the tympanic muscles have been demonstrated in test subjects expecting a strong noise It is often sufficient to tell the patient "You are going to hear a loud noise' Usually he is threatened with a pistol Conditional tympanic muscle reflexes have hitherto not been observed during impedance measurements We have also observed spontaneous and conditional contractions of both the tympanic muscles during operations for otosclerosis

The way in which the inner ear is protected against sudden noise has been subject to speculation for a long time The tympanic muscles do not appear to protect the inner ear during the latency time for the acoustic reflex Demonstration of conditional tympanic reflexes solves this riddle

At the same time we obtain a reasonable explanation as to why an anticipated *noise results in less cochlear damage than an unexpected one*

unpleasant sounds, especially if unexpected, the test subjects react by closing the eyes, and at the same time, contracting the tensor tympani muscle

The contraction of the tensor tympani muscle is thus included as a part of the cochleo palpebral reflex, which has startle characteristics Galambos et al (1953) showed that in man, intensities of 115—140 db re 0 002 dyne/cm² have to be reached before blinking will occur with the majority of click stimuli

Tensor contraction due to voluntary or reflex contraction of the periorbital muscles can be a great help in diagnosing a stapedius paralysis or defects in the ossicular chain, corresponding to the long leg of incus Acoustic stimulation of the contralateral ear using Báránys noise box gives no impedance changes, while voluntary or reflex contraction of the periorbital muscle gives abnormally large impedance changes Audiograms and/or the presence of a facial palsy can help distinguish between these two

Defects in the ossicular chain corresponding to the stapes crurae, give relatively small impedance changes on acoustic stimulation of the contralateral ear, and small or no impedance changes during a blast to the homolateral ear, while voluntary or reflex contraction of the periorbital muscles usually gives greater impedance changes depending on the mobility of the ossicular chain

Acoustic impedance measurements can thus be used both for diagnosis and localisation of a defect in the ossicular chain

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SOUND LOCALIZATION IN FREE FIELD AND INTERAURAL THRESHOLD DIFFERENCES

By

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Abstract

It is a well known fact that the ability of locating sound sources by persons with normal hearing depends on the type of signal. It is moreover a fact that persons with unilateral deafness at least to certain types of signals, lose the ability of sound localizing

Experiments were performed with the intention of making certain the relation between the ability of sound localization in the horisontal plane and the threshold difference between the two ears, one of which had normal hearing The listeners with eliminated visual orientation were placed in different angular positions to the sound source in an anechoic chamber Different types of signals were used The results will be discussed in regard to a practical point of view

The purpose of this work was to determine to what extent threshold differences between the two ears affect the angular localization in the horizontal plane The physical parametres which determine a person's ability to localize a sound source are mainly time, phase and intensity differences between the two ears As was demonstrated by Nordlund (5,6) in his thorough investigations, the time factor was the decisive element in complex sounds, the phase for pure tones under about 1400 cps, and intensity for pure tones above 1400 cps Jongkees and Groen (1) have showed that a sound source from behind is often mistaken as coming from in front, even by persons with normal hearing The same authors damped down transmission through the external ear 15—20 dB with cotton-wool soaked in paraffin wax They found a deviation in localization towards the normal hearing side

We wanted to examine the angular localization when the source of sound was placed alternately on the side of the normal hearing, the side of impaired hearing and behind or in front of a plane through the two ears Pointing deviation and the spread in the observations were determined as functions of the threshold difference and angular position of the head

Fig 1 shows the test set up In an anechoic chamber the blindfolded listener was placed in a swivelchair Around the listener was placed a scale, which was graded from 0° to 200°, positive to the right, negative to the left. The sound source, a single loud speaker was placed at the scale value 0° at a distance of 3 metres from the listener The listener was turned to six different positions ± 30°, ± 70°, ± 130° The pointings were marked off to the nearest 10°

For technical reasons we used a rotatable listener rather than a movable loud speaker Another method, using six loudspeakers in permanent positions, was dropped It was difficult on account of band noise to prevent recognition of the

different loud-speakers by their different pitch 500 cps and 4000 cps pure tones were chosen as stimuli together with 1/1 octave band noise with centre frequency 2000 cps (5,6) The intensity of the signal was varied at random between 55

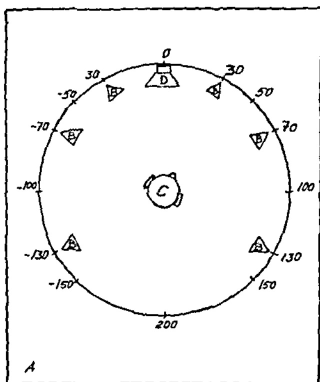


Fig 1 Test set up for measuring the pointing deviation
A Anechoic room B Angular position C Listener D Loudspeaker

and 70 dB (re 0 0002 dynes/cm²) so as to avoid *recognition of the signal* According to Nordlund (6) intensity variations between 20 and 80 dB are not of importance to people with normal hearing Varying threshold differences are in most cases procured by supplying the one ear with different kinds of ear protectors In some cases, however, persons with either unilateral conductive impairment or unilateral complete deafness were tested Threshold differences were determined by means of pure tone audiograms without protection and by means of free field measurements The listener was turned in the chair. Disorientated with regard to his angular position he was brought into one of the six positions and the signal was given The listener (without moving his head) pointed to the place from where he believed the sound originated The degree mark on the scale at which he pointed was noted

The chamber does not quite meet the demands of a free field, but the reverberation time is well under 0 2 seconds Measurements on persons with normal hearing showed however, on the whole, the same degree of accuracy as that described in the literature on similar tests (1, 2, 6) We therefore considered the room satisfactory Special precautions have been taken to procure a minimum

of clicks when switching on and off the pure tone signals As to the band noise special precautions on this point have not been taken The clicks were, however, not recognizable The experiments were repeated with several threshold differences for some of the listeners Other listeners were tested with one or two threshold differences In a few cases the same experiments have been repeated some days later The results were reproducable As a measure for pointing deviation (with varying both threshold differences and angles), the mean value of the noted pointing direction was taken The spread in the material was expressed in standard deviation

For persons with normal hearing, the results were of the same order as those found in other experiments

The results from the six positions showed no variation to the applied signals The results from persons with unilateral deafened ears were dependent on the applied stimulus

Fig 2 shows pointing deviation as a function of angular position for 4000 cps The tendency to point towards the side of the normal ear increased with increasing threshold differences The pointing deviation therefore showed a shift when the sound source was on the deafened side

In figure 3 the results from position —70° illustrate how pointing deviation increased with increasing threshold differences The individual variations were considerable The threshold difference which was necessary to cause a significant reduction in directional hearing varied

For the signal 500 cps the material is not so comprehensive It was difficult to attain sufficient damping Nevertheless these results showed the same tendency as did the results from the 4000 cps experiments

For 2000 cps band noise the material showed no corresponding changes of

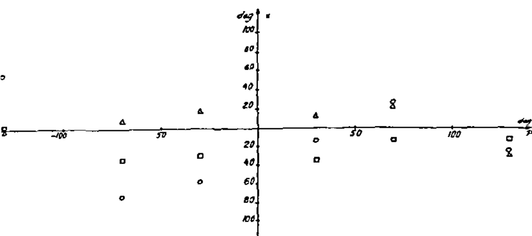


Fig 2 Pointing deviation as a function of the angular position Stimulus 4000 cps pure tone Left ear normal.

△ Threshold difference 0— 5 dB
□ Threshold difference 20—25 dB
○ Threshold difference 40—45 dB

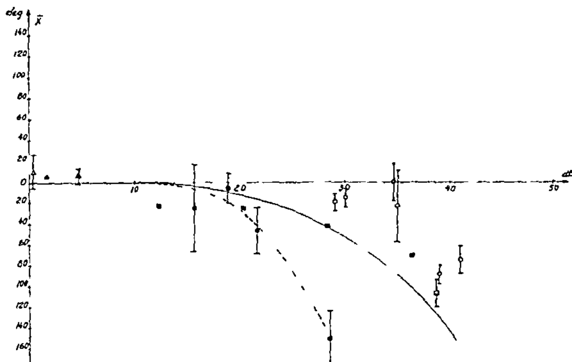


Fig 3 Pointing deviation as a function of interaural threshold difference Stimulus 4000 cps pure tone The fully drawn curve shows the median for the complete material The two other curves are representatives for individual persons

directional hearing for differences under 30—40 dB The effect was, on the other hand, proved for higher threshold differences

As a curiosity can be mentioned, that one person with unilateral complete deafness showed a tendency to point to the deaf side on being presented a 2000 cps band noise

The results of the experiments with 500 cps pure tone showed a special effect Jongkees and Groen (1) found a tendency to point to a mirror image of the sound source in front, when a stimulus of 1000 cps was presented from behind In our material the listeners had a tendency to point behind when the threshold difference increased, independent of the position of the sound source This effect can be seen in figure 4 The same effect was not present for the signals 2000 cps band noise and 4000 cps pure tone

CONCLUSION

For the signals 500 cps pure tone and 2000 cps band noise a tendency towards increasing spread was found when the threshold difference increased No corresponding relation between spread and interaural threshold difference for the signal 4000 cps pure tone was found For 4000 cps, however, there was a marked increase in pointing deviation with increasing difference, when the source of sound was on the deafened side The same tendency was found for

the 500 cps pure tone signal, but did not seem to be provable for 2000 cps band noise with threshold differences below 30—40 dB This observation can be explained through the greater amount of information found in complex sounds

The results thus showed that angular localization was inhibited by a sufficiently high mechanically caused interaural threshold difference for the stimuli 500 and 4000 cps pure tones Reduction in angular localization mostly occurred on the deafened side The intensity level differences between the ears, sufficient to influence angular localization were subject to individual variations and usually occurred at 20—40 dB

Using band noise, increased pointing deviation was not provable with threshold differences below 30—40 dB This fact may be importint when fitting mon — or binaural hearing aids in cases with conduction deafness Investigations in order to elucidate this question are now going on

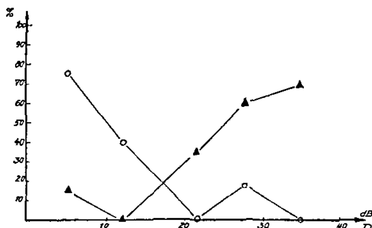


Fig 4 Percentage pointings towards the mirror image of the sound source as a function of interaural threshold difference Stimulus 500 cps pure tone

▲ Angular position 70° (loudspeaker in front)
○ Angular position 130° (loudspeaker behind)

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PATHOLOGICAL FATIGUE IN PART OF THE HEARING NERVE ONLY

By

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Abstract

As far as the tone decay test may be used to demonstrate the existence of pathological fatigue, it is possible to show that such fatigue may be present only in restricted frequency ranges The topological anatomy of the eighth nerve seems to indicate in which fibers such pathological fatigue is most likely to occur This conception is in good agreement with the positive findings of pathological tone decay in certain frequency ranges together with normal conditions for other tones

What I with a physiological term have called pathological fatigue consists of a decay of the tonal perception of a contineous sinusoidal stimulus during a relatively short time (60 seconds), even when the intensity of the stimulus is increased to normal threshold of discomfort The hearing sensation may either disappear totally or the tonal character vanish into a perception of noise

The phenomenon has been studied since Wegel and Lane's masking experiments in 1924 It is, however, escpecially during the last decade that clinicians have been interested in auditory fatigue and made a series of experiments in order to establish a simple clinical test for a quantitative measurement of the phenomenon

In a somewhat more restricted definition of the phenomenon Loss of loudness level of 30 dB or more during continous stimulation of a pure tone, the intensity of which is increased from the threshold of hearing — there has been given different designations

1) A purely descriptive designation

A "Threshold Tone Decay Test" (Carhart 1957), — emphasized by H Sorensen at the last Congress in 1960

B "Temporary Threshold Shift" (Lierle & Reger, 1954), brought into a useful clinical test by P Yantis in 1959, as the "TTS test"

C 'Tone Relaps" — "Pathological Relaps' — "Excessive, abnormal pathological loudness level loss" etc — especially by Dix, Hallpike, Hood, — who in 1950 started to publish a series of papers about their investigation of auditory fatigue

2) A Physiological designation

A Per Stimulatory Adaptation" or "Per-Simulatory Fatigue' (Hood) should be used as interchangable terms

In the literature, however, one has been rather reserved in using the term

"Fatigue" for the phenomenon, and has mainly preferred "Adaptation", as for instance "Abnormal Adaptation", "Pathological Loudness Adaptation" etc

The reason for the reluctance towards the fatigue-designation is probably a specific feature related to this phenomenon If the intensity of the fatiguing stimulus is continuously increased from the threshold of hearing to a level well above this threshold, — however, not perceived by the patient, — and then interrupted for a moment, it will be heard as a loud tone the moment it is switched on In a similar way a periodically interrupted stimulus will keep its loudness level also

Sørensen therefore positively denies the possibility of fatigue in this phenomenon " after interruption of the tone the patient regains his original threshold within a few seconds, consequently the measured tone decay cannot be due to fatigue, which is defined by a decline in excitability caused by previous activity"

This definition of fatigue is probably relevant only to the type of fatigue called *"Post-stimulatory fatigue", thorougly investigated by Davis et al in 1943* The effect of post stimulatory fatigue is certainly more persistent and recovery is much slower than is the case for per-stimulatory fatigue This fact, however, does not exclude the existence of "per stimulatory fatigue"

Using a common definition of fatigue (Webster) "Condition of cells or organs which have undergone excessive activity with resulting loss of power or capacity to respond to stimulation", I find fatigue the most relevant designation to the phenomenon of "tone decay" The diseased organ can stand almost nothing of sustained stimulation before it is completely exhausted and without capacity to respond normally

The term adaptation contains a positive component, its definition is (Webster) "Adjustment of a sense organ to the intensity or quality of stimulation " Adaptation is therefore a useful modification of a sense, making the organism more suitable to meet new environmental conditions and respond adequately to changes in them

The process of adaptation is probably established by a neural feed back system, involving higher neural centers to direct the process, as for instance when musculus stapedius contracts as a response to intense sounds or to complex central activities (Carmel and Starr)

A diseased sense organ may lack the ability to adapt or may use an abnormally long time to adapt However, when in the actual phenomenon the sense organ has "adapted' itself causing lack of ability to respond to regular stimulation, it is probably no longer adaptation but most likely fatigue

The above mentioned publications from Dix, Hallpike and Hood from 1950—55, stated that per-stimulatory *fatigue was "pathognomic of a cochlear lesion"*

Later works of other investigators have had difficulties in confirming this statement It was, however, found that in some cases of cochlear lesions one might see pathological fatigue causing a threshold shift of until 30 db

During the last 5 years continuous work on this phenomenon has changed the conception of what type and location of lesion it indicates Per-stimulatory *fatigue* exhibiting a distinct threshold shift, is considered to be characteristic of

a retrocochlear lesion As says Sorensen "Indicative of functional impairment of the central auditory pathways or the acoustic nerve"

Is it possible that such impairments of the eigth nerve may appear in a restricted part of the central auditory pathways only, — causing pathological fatigue in a limited frequency range?

A possible way to answer this question would be a systematic examination on pathological fatigue in various frequency ranges, i e the threshold tone decay test should be carried out for quite a number of frequencies

It is a sound attitude towards more specific tests of the function of hearing, that they always should be carried out at different frequencies Aware of the different behaviour of the ear for stimuli of low and high frequencies, it is obvious how dangerous it is to base topodiagnostic conclusions upon functional examination at one single frequency

In this paper results obtained by means of the threshold tone decay test carried out at different frequencies, will be presented

The purpose is not only to give an answer to the presented question, but rather to emphasize the problem and point out the possibilities for elucidating various questions of interest to the theory of hearing, and also to suggest the usefullness in topodiagnosis, when a greater clinical material is accumulated

APPARATUS AND METHOD

A Peters SPD 2 audiometer was used

In this audiometer frequency and intensity may be continuously varied without any form for click or interruption The audiometer was calibrated to the proposed international standard threshold (ISO Draft Recommendation No 554)

In connection with a thoroughly audiological examination the threshold tone decay test was applied for a series of frequencies from 250 Hz to 8000 Hz The choice of test frequencies was determined from the audiogram of the patient, his case history, and from his ability to cooperate during a rather tiresome and time consuming examination

Usually the tone was presented to the patient 10 db above his threshold The patient was instructed to keep his finger raised as long as he heard the tone as a tone

When he signaled that the tone had disappeared, the intensity was increased 5 or 10 db at a time until the tonal quality of the signal persisted for at least 60 seconds — or to the maximum intensity of the audiometer was reached (100—110 db)

With more than 50 db difference in hearing loss between the two ears, adequate white noise masking was applied to the better ear

Some tests with and without masking of the better ear indicated that central masking in some cases may introduce a registration of pseudo-pathological fatigue

It is however, very difficult to differentiate between a masked threshold and a centrally induced fatigue

If masking is not used, it will cause cross hearing to the better ear, and positively present pathological fatigue may not be registered Therefore it is very important to use adequate masking in these tests It is also necessary to be consious about the quality of the perception It may happen that the patient is indicating that he hears the tone, but the perception has totally changed, loosing its tonal quality A tone is no longer heard, only a kind of noise is perceived

The amount of threshold shift has been registered either by means of a Bruel & Kjær Level Recorder connected in parallel to the telephone receivers of the audiometer, or by means of the operators observation and recording of the various levels and time intervals of the applied stimuli I find the manual method fully serviceable, especially when the observer uses a watch giving a faint sound each second, making it possible for him to count seconds and constantly observe the patients signal

The duration of the tonal perception at each intensity level is recorded as a fraction, for instance 80/5, 85/3, 90/0 db/sec

In agreement with the diagrams obtained on the Level Recorder, the results of the test have been presented graphically with the duration of the stimulus plotted along the abcissa and intensity along the ordinate (increase of intensity along the positive axis, contrary to what is usually in audiograms, where increase in intensity means increased hearing loss, and is therefore plotted along the negative ordinate axis)

RESULTS

Young persons with normal hearing showed no sign of fatigue as indicated by a vanishing of tones of frequencies 250, 1000, 4000 and 8000 Hz respectively, when presented at a sensation level (S L.) of 10 db

When the intensity was decreased rather slowly from 10 db above threshold, after 80 seconds stimulus time, the tonal sensation seemed to disappear at about 4—7 db S L With this method it was not possible to demonstrate any significant difference between low and high tones in their ability to maintain a stable loud ness level This was not quite true for normal hearing persons above 40 years, who indicated some difference between the lasting loudness of 8000 Hz com pared with the loudness of the other tones A more refined method might perhaps unveil such differences in all cases, the lower tones producing more stable loudness

In most of the perceptive hearing losses examined I have found a threshold shift of about 20 db for frequencies above 1000—2000 Hz, and about 10 db, — or almost the same as for persons with normal hearing — in the frequencies below 1000 Hz This is not considered to be real pathological fatigue

There is a series of exceptions from this rule These exceptions are listed in different groups according to diagnosis and/or response to the test

1 *Tumors of the eighth nerve*

The hearing loss in this disease is progressive and very often the patient comes to our hospital when his affected ear is totally deaf Only 4 patients have been

a retrocochlear lesion As says Sorensen "Indicative of functional impairment of the central auditory pathways or the acoustic nerve"

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In most of the perceptive hearing losses examined I have found a threshold shift of about 20 db for frequencies above 1000—2000 Hz, and about 10 db, — or almost the same as for persons with normal hearing — in the frequencies below 1000 Hz This is not considered to be real pathological fatigue

There is a series of exceptions from this rule These exceptions are listed in different groups according to diagnosis and/or response to the test

1 *Tumors of the eighth nerve*

The hearing loss in this disease is progressive, and very often the patient comes to our hospital when his affected ear is totally deaf Only 4 patients have been

included in this group, having presented such hearing losses that a threshold tone decay test could be carried out

They are all showing results indicating pathological fatigue in the entire frequency range Three of them lost the hearing sensation completely for a prolonged stimulus One had his tonal perception changed into that for a hissing noise (Fig 1 a) His tumor was verified by the surgical treatment This was the case also for the other two patients, whilst the fourth has not yet been operated His audiogram and results of the decay test are presented in Fig 1 b

Five more patients with brain tumor have been examined with respect to threshold tone decay, without precise measurement of the decay function The results, however, were convincingly as to show decay for frequencies in the entire audible range

It therefore seems justified to conclude that in cases of brain tumors affecting the auditory pathway, pathological fatigue may be demonstrated in the total audible range Some reservation may be made for cases of very early stages in the disease, which are not examined in the present work

2 *"Sudden Deafness"*

Four cases of 'Sudden deafness of obscure origin' have been examined with the threshold tone decay test

Three of these cases had audiograms showing rather good hearing for very low tones and a steep increase of the hearing loss towards higher frequencies

The fourth case had a flat threshold curve at about 80 db loss

None of these cases showed pathological fatigue in frequencies below 1000 Hz In the higher frequency range 2000, 4000, 8000 Hz, however, it was a substantial threshold decay (Fig 2)

As pointed out by O E Hallberg and others sudden deafness may be due to miscellaneous causes In many cases the sudden, total or almost total hearing loss may be of more or less temporary character, and the end results some months later may show quite different audiological pictures from completely restored hearing to total deafness The way in which the results of Fowlers balance test vary with duration after the incident, indicates, at least in many cases, that both cochlear and retrocochlear parts are being injured The results of the decay test reported here are interpreted in the same direction, the observed pathological fatigue in the higher frequency range to indicate injury of retrocochlear elements the rather normal threshold decay, associated with recruitment in lower frequencies to indicate cochlear damage

3 *Congenital deafness* (Birth trauma, anoxia)

The audiograms for all six cases in this group, show rather good preserved hearing in the lower frequencies with increasing impairment of higher frequencies

Recruitment is shown to be present at certain frequencies up to about 2000 Hz (with the monaural balance test and/or with the impedance test, aural harmonic test respectively) Pathological fatigue is not found to be present for frequencies

♂ T J 2

Speak Whisper
Notice
Aural Harmonic Threshold
250 (500) Hz 33 dB S.L.
500 (1000) Hz 40 dB S.L.

Case T J Pathological fatigue in left ear, indicated by rapid loss of auditive perception at all frequencies No discrimination of PB words, nor of digits, and almost no pitch discrimination The hatched area shows the uncertainty of the threshold determination

♂ A S

Speak Whisper
Notice
Aural Harmonic Threshold
250 (500) Hz 40 dB S.L.
500 (1000) Hz 50 dB S.L.

Speak Whisper
Notice
Aural Harmonic Threshold
250 (500) Hz 22 dB S.L.
500 (1000) Hz 18 dB S.L.

Case A S Pathological fatigue in left ear, indicated by rapid loss of tonal perception at all frequencies A noisy perception of the pure tone stimulus remained for more than 60 seconds, even when masking was applied to the other ear (M) No discrimination of PB words, but fairly *good score for digits. Almost no pitch discrimination above 250 Hz.*

Fig 1 *Examples from 1 Acoustic Tumors*

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below 1000 Hz, whilst typical threshold decay has been demonstrated in the frequency range above 1500—2000 Hz

In a couple of cases there seems to exist some type of overlapping, i e in a rather narrow frequency band there is indication of both recruitment and of pathological fatigue (See Fig 3, I H) For frequencies lower than this frequency band, only the recruitment phenomenon is present, and for higher frequencies only pathological fatigue is found

This shows how precarious it is to make topodiagnostic conclusions from the result of a cochlear/retrocochlear test performed at one single frequency

At the other hand this overlapping of both cochlear and retrocochlear phenomenon is very interesting in the discussion about the localization of hearing impairment in for instance athetoids (G Flottorp et al, Barr and Klockhoff, J Hall) The results of the threshold tone decay tests and the other audiological findings in group 3, certainly indicate that an injured cochlea may dominate the hearing impairment in a restricted frequency range, whilst in the same ear a centrally located lesion may manifest itself in other frequencies, (and most probably in higher frequencies)

4 *High frequency hearing loss*

The three patients in this group had all a very light hearing loss for low frequencies and a steep increasing loss for higher frequencies, together with lowered upper frequency limit and no indication of recruitment or other cochlear symptoms in the entire frequency range

The etiology of these hearing impairments is unknown The hearing loss started, however, rather suddenly The case presented in Fig 4 showed for a period of two years a slowly progressive hearing loss, which for the last 6 months has been unchanged

The patient was observed suspected of an acoustic tumor, but neurological examinations have not confirmed this assumption

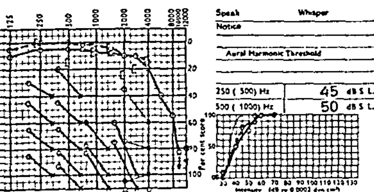
The hearing loss in the other two cases is less pronounced, however, exhibiting the same main features

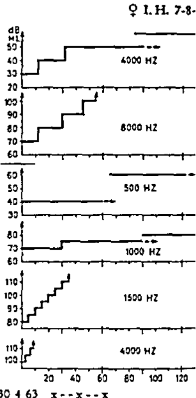
There is pathological fatigue in the frequency range above 1500—2000 Hz, but not in the lower frequencies The loudness of a sustained low frequency tone is however not as stable in the affected ear as in the other, rather normal ear Especially the patient S B Fig 4 reported slowly fluctuating loudness even for 250 Hz, and more pronounced fluctuation the higher the intensity of the tone

CONCLUSION

The results of these examinations using the threshold tone decay test at different frequencies give a positive answer to the raised question Does pathological fatigue exist in part of the hearing nerve only?

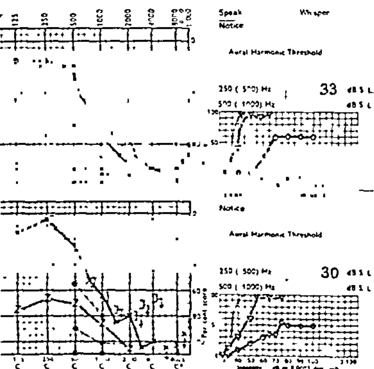
Such fatigue is shown to be present in several cases Common for all cases is the lack of cochlear symptom in the actual frequency range (but for the over





1-2 60 o—o—o x—x—x 19-11-62 o- - o- - o 30 4 63 x- - x- - x

Fig 3 *Congenital Deafness* Case I H . Anoxia is the most probable cause for this hearing loss No pathological fatigue below 1000 Hz, recruitment at 1000—2000 Hz according to the monaural balance test and the impedance test ad mod Metz (z—z—z) and pathological fatigue above 2000 Hz



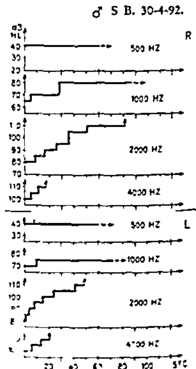


Fig 4 *High Frequency Hearing Loss* Case S B The hearing loss in the left ear was increasing during the two years from 1960 till 1962 and has remained fairly unchanged since then During the active periode there was indication of recruitment in the frequencies at the steep part of the threshold curve No more recruitment now Pathological fatigue in the higher frequencies, however not in lower, has been present all the time during the observation

lapping area mentioned under Group 3) Loudness recruitment for instance has not been found associated with the phenomenon

It therefore seems justified to assume that the presence of pathological fatigue in a restricted frequency range is pathognomic for a retrocochlear lesion of limited extent, unless the common accepted interpretation of loudness recruitment, fatigue etc, should be reconsidered

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VASCULAR SUPPLY OF THE TYMPANIC MEMBRANE AND TI OSSICULAR CHAIN

By

C-A Hamberger and *Jan Wersall*

From the Department of Otolaryngology Karolinska sjukhuset, Stockholm

Abstract

The ossicular chain is partly supplied by nutrient arteries penetrating the bone, and bra into an extensive network of mucosal vessels Although the arteries are usually well vis specimens treated by the injection technique, the mucosal network is more easily and mo liably identified by the staining method used in the present study This network is partic important for vascularization of the processes of the incus and malleus, as far as the st concerned, it is the only source of blood to its footplate

The method used in the present study has proved to be highly suitable for investigat the mucosal blood supply in the auditory ossicles This suggests that it will be of val studies of the circulation in grafts in the middle ear and tympanic membrane

The gross blood supply of the middle ear and the drum membrane is well k through the studies by Moos, Kolmer, Luscher, Hamberger and others The is true for the gross vascular supply of middle ear mucous membrane an ossicular chain where Nager and Nager 1953 published an excellent surv own and others' studies on the vessels

However, little has been written about the fine supply of the drum meml and the vascular network of the mucosa on the ossicular chain We consider problems extremely important from surgical point of view and would like t monstrate the usefulness of the benzidine blood cell staining method for st of the fine vascular supply of the middle ear and the drum membrane discuss a few anatomical findings

The Benzidine Method

For the benzidine method (Sjostrand) the specimens are fixed in for following which they are exposed to a solution containing benzidine, alcoho hydrogen peroxide The benzidine stains the blood cells in the capillarie gives an excellent view of the capillaries as well as larger vessels in the spec By careful dissection any part of the middle ear can be exposed to the sta solution and the vascular supply easily studied

Membrana Tympani

The vascular supply of the drum membrane is derived from both externa internal sources Authorities differ as to the origin of these vascular cha although they agree on the general plan of vascular network and the inte munication of external and internal systems Two dominant plexuses m distinguished that of the hammer handle region and that of the vascular around the perimeter

The *inner surface* of the membrane is supplied by the following vessels

1 a twig from the middle meningeal artery, and
2 the vascular circle formed by
   a) the anterior tympanic artery from the internal maxillary which enters the middle ear through the petrotympanic fissure along the exit of the chorda tympani
   b) the posterior tympanic artery a branch of the internal maxillary entering the middle ear along with the chorda tympani and

[illegible]

from

the

Studying the fine anatomy of the small arterial branches in the drum membrane we find that these arteries do not divide dichotomously as earlier described but form complicated whirls and semicircles with an extremely rich anastomosing system (Figs 1—2)

With the benzidine staining method where the blood cells are darkly stained it is easy to see the vessels through the drum membrane The dominating vessels are not the arteries but the fine meshed network of small venules The branches formed by the confluence of these small venules are several times thicker in the pictures than the arteries

Even the venules anastomose and form loops and curves on their way over the surface In some specimens the vessels cover up to one half of the total surface seen and dilated the vessels might be thicker than the spaces between them

One problem which we tried to solve in the study are shape and distribution of the connections between the arterioli and the venuli We found, as illustrated in Fig 2 that small capillaries leave the arterioli Some of these are in direct communication with the venuli Other capillary vessels form an extremely well developed network of capillaries with polygonal meshes between arteries and veins

It is of course difficult to demonstrate through the observations of histological specimens any directional flow of the blood The arrangements of the vessels seem to support, however the idea that the blood flows via the arteries along the handle of the malleus from there out to the oblong meshes of the capillary network in the drum membrane and further out to the periphery of the membrane where it goes through the rich vein plexus in the veins passing in different directions along with the above mentioned arteries As the veins are found concentrated on the internal side of the drum membrane it seems most likely that a large part of the outflow takes place through the veins of the middle ear

Earlier publications have generally stressed the fact that the flow of the blood through the drum membrane takes place mainly through radial arteries passing from the malleolar fold towards the periphery of the drum membrane Section of these arteries would then cause ischaemia in an area of the drum surrounding the defect Our study shows that the network of loops in the drum membrane is such that only very large and irregular defects would cause any important change in the blood flow as anastomosing vessels would immediately take over where

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Abstract

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However, little has been written about the fine supply of the drum membrane and the vascular network of the mucosa on the ossicular chain We consider these problems extremely important from surgical point of view and would like to demonstrate the usefulness of the benzidine blood cell staining method for studies of the fine vascular supply of the middle ear and the drum membrane and discuss a few anatomical findings

The Benzidine Method

For the benzidine method (Sjostrand) the specimens are fixed in formalin following which they are exposed to a solution containing benzidine, alcohol and hydrogen peroxide The benzidine stains the blood cells in the capillaries and gives an excellent view of the capillaries as well as larger vessels in the specimen By careful dissection any part of the middle ear can be exposed to the staining solution and the vascular supply easily studied

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some vessels are cut This finding is well supported by the clinical findings that even large traumatic defects in the drum might heal very quickly provided remaining flaps of the drum membrane are brought together by apposition Only short lasting ischemic reactions will occur due to the reaction in the surrounding vessels The method is now used for studies on the healing of wounds in the drum membrane

Middle Ear

As recently stated in a study by Anson and co workers the bones of the ossicular chain are composed of nonhaversian bone The vascular channels thus do not follow the structural pattern of standard skeletal parts Their location within the middle ear cavity provides little contact and no direct connection with the surrounding bone The bones of the ossicular chain depend on vessels passing through mucosal folds or ligam nts of the middle ear cavity for their vascular supply

Nager and Nager described the gross vascular supply of the ossicular chain

The ossicular chain is supplied by branches from the anterior and posterior

rom the anterior fold to the head of the malleus where it penetrates into the bone through a nutrient foramen Often this vessel branches several times before disappearing in the bone One artery goes along the anterior process to the neck of the malleus where it penetrates the bone and forms several small branches one of which passes inside the handle of the malleus This is a thin tortuous vessel Several branches split up into a complicated mucosal network of arterioli which in turn form a capillary network in the mucosa covering the surface of the bone This network anastomoses in several places with the intraosseous vessels

In sections through the malleus several channels are observed within the head of the malleus, containing rather wide arteries and veins (Fig 3) The handle of the malleus is less well supplied and it seems as if the mucosal capillary net work might be of importance for the supply of the handle of the malleus (Fig 4)

The *incus* receives its blood supply from three small arteries One branch goes into the body of the incus close to its articulation with the malleus It comes from the superior branch of the anterior tympanic artery One branch supplying the body and the long process of the incus is a long tortuous vessel passing in a mucosal fold from the anterior tympanic artery on the lateral side of the incus to its entrance in the bone One smaller branch comes via a mucosal fold from the posterior branch of the anterior tympanic artery

All these vessels form intraosseous branches and communicating twigs which are connected to the dense mucosal network Neither the methods of Nager and Nager nor that of Anson and co-workers which both depended on reconstruction of series of sections from temporal bones allowed for a complete picture of the *extremely rich network found especially in the mucosa covering the ossicles.*



Fig 1 Benzidine staining of the tympanic membrane showing the distribution of the arteries and veins The latter appear thicker

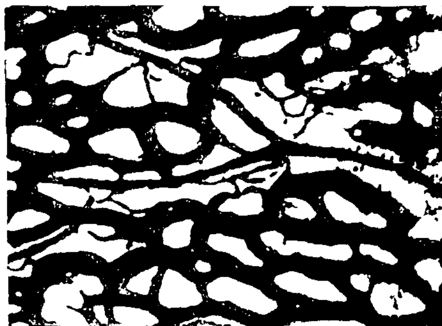


Fig 2 Higher magnification of an area from the same specimen

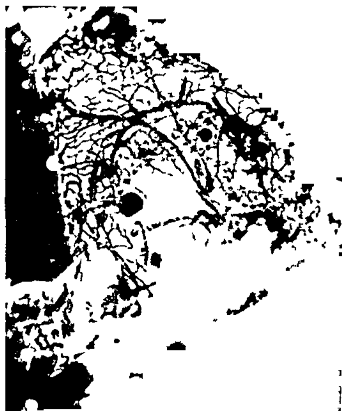


Fig 8 Benzidine stained stapes which demonstrates the rich network of communicating vessels on the surface of the stapes as well as the connections between the posterior crus and the anterior crus and the vessels down to the foot plate

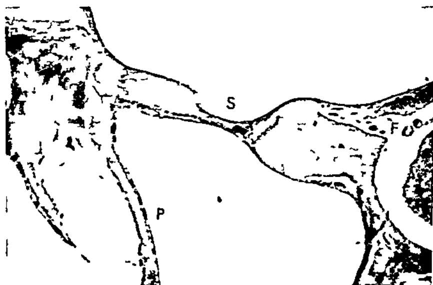


Fig 9 A section through the facial canal (F) showing the vessels leaving the canal and passing along the stapedius tendon (S) to the head of the stapes P posterior crus.

This network of vessels is very elaborately visualized with the use of benzidine staining of the blood cells within the vessels, as used in the present study (Fig 5)

In the long process of the incus this vascular supply is not always well developed, and the intraosseous vessels might be extremely thin (Fig 6) This is especially true for bones from ears with known previous infections It seems that under infectious action on the bone this is easily sclerosed with partial obliteration of the vascular channels In these cases in particular the mucosal blood supply seems to be of extreme importance for the survival of the bony tissue in the long process The decalcification sometimes seen in the long process of the incus is likely to depend on an insufficient blood supply

Any strangulation of the vessels in the mucosa or scraping of the mucosa from the incus then might entail a risk of degeneration of the long process of the incus

The *stapes* differs from the other two bones in the ossicular chain as to the intraosseous blood supply

Only the head of the stapes contains normally intraosseous vessels of any calibre The crura and the foot plate might be completely devoid of blood vessels within the bony substance and entirely depending on the mucosal arterioli and capillaries for their blood supply

Only in cases with unusually thick crura or foot plates or in stapeses with otosclerotic changes is a more advanced intraosseous blood circulation developed

Also the stapes may be more prone to damage of its vascular supply by infectious processes or manipulations in the middle ear than the other two ossicles This depends on the fact that the main vessels supplying the stapes come from the stylomastoid artery (Fig 7) The small arterioli from the stylomastoid artery follow mucosal folds from the facial ridge over to the stapes or pass along the stapedius tendon From here some branches pass over to the anterior crus via intercrural folds Some of the small branches pass upwards the head of the stapes, where they intercommunicate with branches from the opposite crus and from the mucosa of the articulate process of the incus (Fig 8) The footplate area is covered by a mucosal layer richly supplied with arterioli and veins The arterial

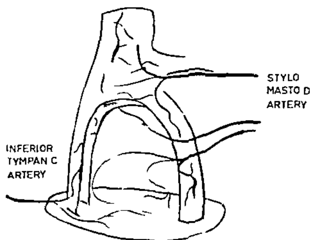


Fig 7 A schematic drawing of the blood supply to the stapes which comes predominantly from the stylomastoid artery through vessels following the stapedius tendon and vessels passing through mucosal folds between the facial canal and the posterior crus of the stapes The anterior part of the foot plate is partly supplied by the interior tympanic artery

SOME HISTOLOGICAL EXAMINATIONS OF THE INCUS AND STAPES WITH ESPECIAL REGARD TO THEIR VASCULARIZATION

By

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Abstract

On account of the frequent discovery of degenerative phenomena of the long process of the incus, especially in cases of chronic otitis it is presumed that this degeneration is caused by nutri tive failure due to local vascular disease

Histological examinations of the incus and stapes with serial sections have been made with the particular intention of demonstrating the vascularization of these bones

Modern oto-surgery has shown that the *long process of the incus represents a* locus minoris resistentiae"

During operations in which chron otitis is the indication for operative treatment one can often see an interruption of the ossicular chain due to necrosis of the long leg of the anvil At the same time one can observe that the stapes, despite its delicate construction, appears to be whole and unaffected It would *seem that there is a certain frailty about the long process also in cases where it is* not exposed to the trauma concurrent to chronic infectious otitis, but *exclusively* to mechanical stresses This is most clearly seen in otosclerosis surgery when one can find that the cause of unsatisfactory results of the operation is an interruption of the ossicular chain due to necrosis of the processus lenticularis One has *seen this develope even in cases of cranial fractures*

E Muller has found the following on examination of 100 operated ears

Table I *The high incidence of necrosis of the incus found during operations for chronic otitis media*

Disease	Total loss of the incus	Necrosis of proc long incudis	Sum
Chron c serous catarrh	0	0	2
Chron otit without bone affection	4 (17%)	7 (29%)	24
Chron otit with bone affection with out cholesteatoma	4 (4%)	7 (41%)	17
With cholesteatoma	28 (38%)	4 (7%)	57

It would therefore seem reasonable to seek the cause of the anvils vulnerability *in a compromised nutrition of the bone due to disturbances of its* vascularization

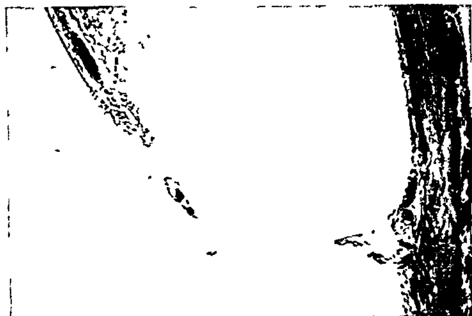


Fig 13 This picture demonstrates connections through mucosal folds between the crura of the stapes



Fig 14 The foot plate (Fp) has no vessels in the bony substance but is dependant on the mucosal vessels (C) Some of these come as shown in the present section, from vessels along the crura

in the folds of this membrane, which have not the character of adhesions, between the long process and its surroundings No variations of the structure of the incus have been observed either in cases with a well pneumatised mastoid process or those without pneumatisation

Stapes In serial sections, 10 u thick 377, cut across the long axis the vestibular part of the footplate is seen to consist of clear polygonal cartilage-like cells which further lateral are replaced by thin boneplates of the usual histological construction In this bone tissue are seen small vessels in the central part of the footplate, but in the more thickened area anteriorly and posteriorly, where the crura is attached the vessels are particularly prominent In the basal part of the crura small vessels are seen which continually decrease in size until at a distance of 0 2 mm from the footplate no vessels can any longer be observed In this specimen the crura is found to be without vessels until both crus run together laterally Here once again small vessels can be seen in the ossicle No prominent foramen nutric are found in the vicinity of the attachment for the m. stapedius, but the mucous membrane around the stapes in this area is well vascularized and particularly in the area of the cranial surface of the capitulum stapedii, that is to say in the angle between the stirup and the long process of the anvil In sections where the stapes is cut along its long axis small vessels as mentioned

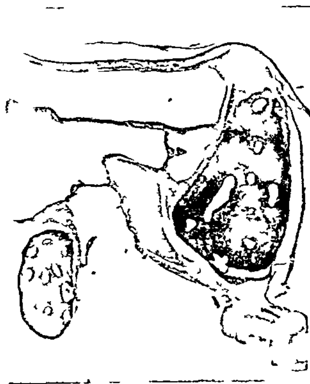


Fig 2 Photomicrograph × 25 Manubrium with the membrana tympani chorda tympani and long process of the incus, showing folds of the mucous membrane containing vessels.

blood supply to the middle ear and the ossicles They found that the anterior tympanic artery was the most important vessel to the malleus and incus and that a branch from this artery, which they called the ossicular artery, divided into two branches for the malleus and incus With regard to the branch to the incus they found that it usually entered the ossicle in close proximity to the



Fig 6 The footplate of the stapes Photomicrograph × 25 showing a tiny vessel in the bone in the central region of the plate

joint capsule, then dividing in cranial and caudal directions to supply the different parts of the ossicle Nager and Nager find further that the mucous membrane over the incus and incudostapedial joint is well vascularized but that only seldom does one see that these vessels penetrate the corticalis

With regard to the stapes they found that its anterior part is mainly supplied via branches from the superior and inferior tympanic artery, while the posterior part is supplied by vessels which issue from the fascial nerve canal, branches of the superficial petrosus artery Only exceptionally does one find vessels in the crura stapedii and that the crura only receive their nutrition via vessels in the mucous membrane

In their description of the blood supply to the anvil Nager and Nager have found that it mainly receives only one solitary artery In my own specimens I have not in any single case found this condition, on the contrary the ossicle is supplied through several larger and smaller vessels which certainly to a great extent penetrate the corticalis in the corpus area, but one can also see small vessels from the mucous membrane penetrate and supply the bone in its more periferal areas

Anson et al have recently published a work about the vascular anatomy of the auditory ossicles and finds that the blood supply to the stapes and long process of the incus has two main sources 1) posteriorly from the fascial nerve canal and 2) anteriorly from vessels which supply the promontorial mucosal membrane The vessels derived from an anterior source do not follow the wall to the stapedial base They leave the wall while remaining invested in a fold of mucosa as they cross the annular ligament to the anterior crus Therefrom they diverge to pass in both directions along the ossicle, to supply the incudo stapedial joint and the stapedial base The posterior supply comes mainly from

vessels in the facial nerve canal, vessels from the stylomastoid branch of the posterior auricular artery The vessels leaving the facial canal emerge just above the stapedial tendon and cross it to the head of the stapes The tendon is covered with branches of this vessel Other vessels from the posterior source follow the mucous membrane to the posterior crus in the same manner as to the anterior crus Vessels from the incudostapedial joint follow both crura to the footplate to anastomose with other vessels in this region, and in this situation the vessels occupy the channel produced by erosion of the obturator wall From the investigation of Anson it would seem reasonable that the blood supply along the stapedial tendon is the most important for the vascularization of the head of the stapes, the joint, processus lenticularis and the distal area of the long process of the incus Consider the so-called "physiological stapedectomy" in which one attempts to save the stapedial tendon in order to insure nutrition of the processus lenticularis (Farrior)

Anson says further that the ossicles together with the pars petrosa of the temporal bone are built up quite differently from the rest of the skeleton in that he does not find any Haversian canals But in my own specimens one can see both in the malleus and the incus as well as in the bone which surrounds the tympanic cavity the ordinary construction of compact bone with numerous Haversian canals With the stapes it is difficult to be certain because of its minute dimensions, but even here there would seem to be Haversian canals at least at those points where the ossicle has a reasonable thickness, i e at the head of the stapes and at the attachment of the crura to the base Anson also maintains that those vessels which accompany the mucous membrane of the medial wall of the tympanic cavity to the stapes split up and enter foramina in the bone. In the sections I have made one seldom sees vessels in the crus itself One observes them either quite near the footplate or collum, while the intermediate area completely lacks vessel

Conclusion With regard to the incus it receives mainly its blood supply via vessels which enter the ossicle at its most voluminous area — the body — and it seems to have its foramina nutricia particularly on the medial side of the body

That variable folds in the mucous membrane, which histologically do not appear as adhesions, and containing many vessels, also play an important part in the blood supply especially to the long process of the anvil seems certain

No differences in bone construction, the vessel luminae and their size and number in the long process of the incus can be seen when compared to the same dimensions of the malleus

With regard to the stapes one finds vessels in the footplate as well as in the crura close to the base, but it is the exception to find vessels in the crura itself In the collum one sees tiny vessels in the bone and in the head of the stapes The blood supply seems to be like that found in areas of the same dimensions in the other ossicles

With regard to the problem which gave rise to this examination, namely what the cause might be of the comparatively frequent degeneration of the long process of the incus it should seem reasonable that this can be explained as a failure

in the blood supply of the ossicle We have 2 particular conditions which must be explained

1) Necrosis in connection to chronic inflammation in the tympanic cavity
/ 2) Necrosis after previous stapedectomy

Ad 1) A chronic infection in the epitympanal space will naturally affect just this area which conveys the main bulk of blood vessels to the incus in such a way that the blood supply is compromised

Ad 2) An interruption of the mucous membrane to the incudostapedial joint will lead to a failure in the blood supply to the caudal part of the long process with consequent necrosis of its distal area

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PATHOLOGICAL STUDIES IN PERCEPTIVE DEAFNESS

FOUR PATIENTS WITH PRESBYACUSIS

By

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Abstract

In patients with known perceptive hearing loss we have studied the pathological changes in the labyrinths and auditory pathways in the brain stem and hemispheres

The patients were divided into two groups one in which perceptive hearing loss was confined to the high frequencies, and another in which considerable hearing loss for low frequencies was associated with severe hearing loss for high frequencies

We intend to discuss the pathological basis for the difference in hearing loss in the two groups of patients

The present paper is a preliminary report of the findings in four patients who are included in a series of 14 patients in whom we compare the clinically observed hearing loss with the histological findings in the temporal bones and the brain

The conclusions which we draw now on the basis of these four patients may possibly not hold when we have analysed the entire series

The study is the result of a team work, in which Professor H K. Kristensen has kindly had the temporal bones sectioned and stained in his special laboratory at Rigshospitalet, Copenhagen A brief account of the case histories of the four patients is given below

CASE REPORTS

Case 1 — A woman, aged 91 whose past history was essentially that of good health died after cardiac disease of one month's duration At the age of 19, she had suffered from otitis media for a short period, but she did not remember on which side For periods, she had had discharge and impaired hearing, which later disappeared completely

During the last eight years of life, she was troubled by constant hearing impairment At the age of 86, a hearing aid was issued to her at the State Hearing Rehabilitation Centre, Aarhus Examination here revealed severe bilateral impairment of hearing, especially in the left ear and most pronounced for the high-frequency range Rinne's test was negative in the left and positive in the right ear There were no acute signs of otitis media in the left ear

Three weeks before death the patient was subjected to audiometry in the Infirmary of the local Home for the Aged Severe bilateral hearing impairment for low tones was revealed, most pronounced in the left ear, and complete loss of hearing for the highest frequencies was found on both sides Rinne's test was repeatedly positive in both ears, and Weber's test did not show lateralisation The tympanic membranes were slightly thickened, but did not show any defects

Case 2 — A woman, aged 80 who during the last six years of life suffered from arterial hypertension and for the last six months also from cardiac incompensation, died from coronary occlusion During the last six years the patient had also suffered from chronic lymphatic leukaemia

During the last eight years of life slightly impaired hearing was present, but the patient did not want to have a hearing aid During various hospital stays because of the leukaemia she was examined at the State Hearing Rehabilitation Centre, Aarhus, where a symmetrical hearing impairment of perceptive type was revealed The impairment was relatively pronounced in the low frequency range (40—50 db) and of the same severity in the high frequency range up to 4000 cps, while a symmetrical hearing loss of 70 db was observed at 8000 cps Rinne's test was positive in both ears, and Weber's test did not show lateralisation

Case 3 — A man, aged 79, died from coronary thrombosis and pulmonary embolism Since the age of 38, the patient had been admitted to hospital with bronchitis and asthma like symptoms on seven occasions The patient had been a cooper by trade, and had worked in noisy surroundings from his 14th to his 70th year He had never had otitis media It was difficult for him to say how long the impaired hearing had troubled him, but he estimated that it was some where between 25 and 40 years He had been examined four times at the State Hearing Rehabilitation Centre, Aarhus On each occasion, symmetrical hearing loss for high tones had been disclosed, the last two examinations had shown some assymmetry of the audiogram from 500 cps upwards, while symmetry was present at 250 cps Rinne's test was positive, and Weber's test showed lateralisation towards the better (right) ear

Case 4 — A man, aged 88, who had for two years shown clinical signs of nephrosis and heart disease, died from arteriosclerotic cardiac failure The patient had had no complaints of ear disease o impaired hearing, he had never had otitis media, and had never worked in noisy surroundings About three weeks before death audiometry was performed in the Infirmary of the local Home for the Aged. Bilateral symmetrical impairment of hearing of the perceptive type was revealed The impairment was only slight within the low frequency range, while complete loss was observed at the frequencies 6000 and 8000 cps

HISTOLOGICAL STUDIES OF THE TEMPORAL BONES

Organ of Corti — The assessment of the degeneration here is so difficult that we cannot as yet draw any definite conclusions All four patients showed flattening of the epithelium and supporting cells of the organ of Corti The basilar membrane showed no abnormalities It should be noted that in none of the pa

tients, were the vascular changes in the stria vascularis and modiolus so severe as those observed in the cerebral vessels or the vessels passing through the internal auditory meatus

Spiral ganglion — Three of the patients showed moderate loss of ganglion cells in the basal coil of the cochlea, decreasing through the basal to the apical coil In the fourth patient — the one with occupational[1] deafness — the greatest loss of ganglion cells was observed in the basal coil The changes were assessed to be of the same severity on the left and the right side in all four patients

Acoustic nerves — In the peripheral part of the acoustic nerves, the three patients showed relatively slight degeneration and loss of myelin sheaths and axons, while the patient with occupational deafness revealed severer pathological changes The central part of the acoustic nerve is here referred to as the glial part because it in its composition is similar to the white matter of the brain and has oligodendroglial cells along myelin sheaths, while the peripheral part of the cranial nerve has Schwann cells In all four patients, this glial part showed severe pathological changes, also as compared with the peripheral part, viz pronounced loss of myelin sheaths and axons and advanced degeneration once more especially in the patient with occupational deafness It was a striking feature that the Scarpa ganglion and the vestibular nerve were practically normal in all four patients

Ventral and dorsal acoustic nuclei — In the three patients whose hearing impairment was relatively slight for low tones and severe for high tones, the degeneration was estimated to be severer in the dorsal than in the ventral nucleus In the fourth patient, in whom the hearing loss was of equal severity for low and high tones, the changes in the two nuclei were of the same severity and identical on both sides

It was assessed that the loss of ganglion cells and degeneration in the inferior colliculus and corpus geniculatum mediale were equally severe in all four patients

The auditory paths through the brain stem showed degeneration in all four patients, but it was difficult to assess the severity On the basis of this small series, the clinical hearing loss cannot be correlated with the changes in the brain stem, although the histological observations are suggestive of such a correlation with the hearing loss for low tones All four patients showed focal loss of ganglion cells and degeneration in the auditory centres of the temporal lobes but no or only slight satellitosis The white matter was thinned and markedly degenerated

All four patients revealed vascular changes in the leptomeninges, brain stem and cerebrum Grossly, three of the patients showed moderate atherosclerosis of the vessels of the circle of Willis, while practically no atherosclerosis could be demonstrated in the fourth patient, who nevertheless showed the most pronounced cortical atrophy Histologically, all four patients showed in addition to atherosclerosis severe arteriolosclerosis and capillary fibrosis The changes observed in the brain were partly due to advanced age partly sequelae of the vascular alterations as no other disorders of the central nervous system or organs were demonstrated

CONCLUSIONS

On the basis of a comparison of the histological findings in the temporal bones and the brain it must be concluded that the pathological changes, which were symmetrical, were severest in the central nervous system, in particular, in the glial part of the acoustic nerves and the cerebrum Accordingly, it seems as if the hear ing loss should be explained not only on the basis of the pathological changes in the temporal bones, but also, and perhaps particularly, as a result of the degenerative changes in the brain

In the paper to be read, the study is documented by four audiograms and 16 photomicrographs from the temporal bones and the brain

ON THE NEUROPATHOLOGICAL CHANGES IN THE CENTRAL NERVOUS SYSTFM FOLLOWING NEONATAL ASPHYXIA

WITH SPECIAL REFERENCE TO THE AUDITORY SYSTEM IN MAN

By

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Abstract

The role of asphyxia in the ethiology of neurological defects in the newborn is steadily becoming clearer It is now considered a well established fact that asphyxia is responsible for a number of neurological and physiological disorders in childhood, and its neuroanatomical consequences are well known The increasing knowledge of the somatotopical — and in the auditory system also the tonotopical — organization of the brain has added materially to the understanding of the effects of asphyxia. In different brain structures degenerative changes have been demonstrated The present investigation shows, that in the cochlear nuclei a selective vulnerability to asphyxia can be demonstrated qualitatively as well as quantitatively

Neonatal asphyxia is a common condition 4 8 % of liveborn children are reported suffering from asphyxia by Keith and Norval (1950) and 2 8 % by Mørstad (1953), whose large material included 44533 deliveries It was found to be the chief cause of perinatal deaths in 58 % of the cases by Clifford (1941) and in 33 7 % by Corner and Anderson (1958) The sequelae of this condition are numerous Organic cerebral lesions, mental defects or decrease in mental status, low I Q or decrease in intellectual performance are reported in the literature

According to Nielsen and Courville (1951) probably more than 50 % of all cases of essential epilepsy are the results of birth injury or asphyxia, and 55.2 % of cerebral palsied children had anoxia during labour or delivery as the only plausible cause of the condition (Corner and Anderson 1958)

It seems evident that the cells of the central nervous system are particularly sensitive to hypoxia Due to improved methods and refined equipment also clinical reports concerning special senses like the auditory function now are becoming numerous It is found through audiometry in preschool children, that there are more congenital deaf children than can be explained by hereditary, toxic or infectious diseases commonly known to affect the hearing Several investigators have found, that neonatal asphyxia also should be taken into consideration as an ethiologic factor In cerebral palsied children where an anoxic ethiology might be suspected, 20 % were reported having serious hearing defects by Fisch (1955) and 17 % by Barr and Nockhoff (1959) In his report of 250 cases of congenital deafness Fisch (1956) found that 24 % of the children showing a gently sloping audiogram and 51 % of those showing a sharply

sloping audiogram had an ethiology of kernicterus, hemolytic diseases or asphyxia

The localisation of the damage inflicted upon the auditory system by asphyxia has been in dispute Both Barr and Klockhoff and Fisch find the audiometric tests pointing to a central lesion while Flottorp et al (1957) explain the audio metric changes as being of cochlear origin An evaluation of these conflicting results is one of the aims of the present investigation

The clinical findings of the effects of asphyxia on the auditory function are confirmed experimentally, both in man and in animals In man two methods are generally used, either inspiration of a low oxygen athmosphere through a mask, or breathing an oxygen dilution in a sealed steel chamber Both Spiesman and Gellhorn (1935), Klein (1958), and Klein et al (1959) found an increase in the hearing threshold when a 7—11 % oxygen mixture was inhaled through a mask

Applying a sealed steel chamber, Seitz and Smith (1942) found a decrease in speech intelligibility when the oxygen tension simulated a height of 18500 feet, and Smith (1948) found a reduction in general effectivity, including the auditory reflexes, at 10000 feet On the other hand, no decrease in pitch and loudness discrimination or in absolute auditory threshold was found by Consolazio et al (1947) after 12 % oxygen breathed for as long as 72 hours Also an unchanged auditory acuity was found when arriving at 15000 feet of height and after staying there for 30 minutes Following inhalation of pure oxygen at that height however, the auditory threshold increased Thus, the literature indicates that hearing acuity will decrease if the subject inhales oxygen deficient air long enough, when the percentage of oxygen is low enough

In animal experimentation most of the reports deal with the state of the cochlea, electrophysiologically or histologically, in either case with somewhat conflicting results The cochlear potentials are very resistant to anoxia in cats (Lawrence and Wever, 1952, Gulick 1958) While Falbe Hansen et al (1958) found a reduction of the potentials in guinea pigs Lawrence and Wever as well as Maffei and Marcucci (1955) found severe degenerations in the cochlea in cats and guinea pigs, respectively, whereas Falbe Hansen et al did not find any degenerations in the cochlea of their guinea pigs

As regards the central auditory pathways, Windle and Becker (1943) and Windle (1944) in his comprehensive experimental investigations in guinea pigs and monkeys found neuronal changes in the geniculate bodies and the inferior colliculi In man, however, histological investigations of the effects of asphyxia on the central auditory pathways are practically lacking

The present investigation is an attempt to fill this gap by histological examination of the internal ear and the central auditory pathways in new born and premature babies, fatally asphyxiated

60 brains were investigated from corpses perfused with Heidenhain Susa fluid or formalin 50 of these were fatally asphyxiated, mostly premature babies and 10 were controls The organ of Corti, the cochlear nuclei, the inferior colliculi, the medial geniculate bodies and the auditory cortical area were invest

igated For experimental investigation of the problem 62 kittens were used, 32 served as controls, and 30 were asphyxiated Seven were premature, delivered by Cesarean section

The microscopical examination did neither reveal unequivocal pathological changes in the cochlea of babies nor in the cochlea of kittens Several of the preparations showed artefacts probably produced during the preparation, but in successful preparations obtained by improved methods, the organ of Corti appeared quite normal (Fig 1) A B

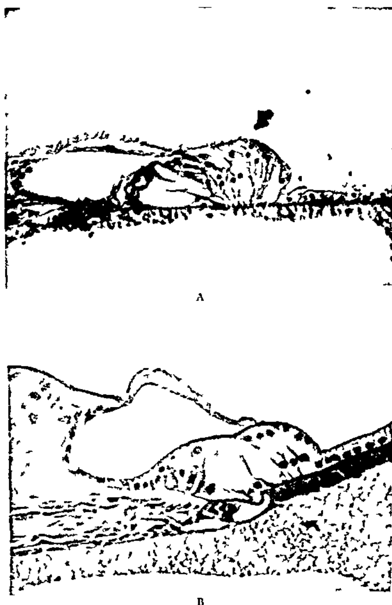


Fig 1 The organ of Corti in asphyxiated human (A) and kitten (B)

In the asphyxiated human cases, changes were found in different parts of the brain stem Of special interest in connection with the present investigation are the changes encountered in the cochlear nuclei They were identical with those described by Nissl as "acute swelling" and "severe cell degeneration". In the acute swelling the cell was enlarged with poorly stained cytoplasm, dissolving Nissl substance and eccentrically displaced nucleus In the cases exposed to

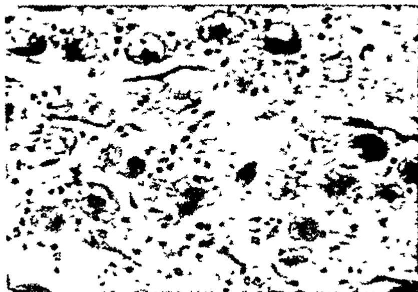


Fig 2 Severe cell changes in the cochlear nuclei

asphyxia for longer periods severe cell degeneration was a characteristic feature of the histological picture The cytoplasm of the enlarged cell was vacuolized, the cell borders blurred the Nissl substance disintegrating and the nucleus dissolving In the most severe cases various "Ghost cells" and cell remnants dominated the picture (Fig 2)

More seldom Spielmeyers (1922) ischaemic cell degeneration was found. A shrunken and intensely stained cell body, containing a few vacuoles and a small dark nucleus

Cell changes were also observed in some of the other auditory relay nuclei, especially in the superior olives and the inferior colliculi, but nowhere so striking as in the cochlear nuclei

To provide a numerical expression for the affection of the cochlear nuclei, the cells of these nuclei were counted The method is described elsewhere (Hall, 1962) This counting gave the following result (Fig 3)

The statistics employed are shown in Table I

It is evident that a loss of cells has taken place and that this loss increases with intensity and duration of the asphyxiation

In the asphyxiated kittens where, as mentioned before, the inner ear looked

normal, the cochlear nuclei likewise appeared normal In each case the number of cells were counted, but no statistically significant difference was found between the number of cells in the 30 asphyxiated kittens and the 32 controls

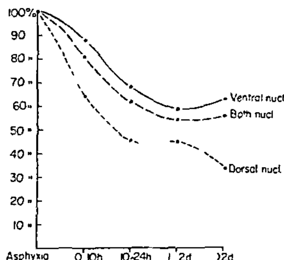


Fig 3 Loss of nerve cells in the cochlear nuclei in cases of asphyxia neonatorum, in relation to duration of asphyxia

DISCUSSION

In asphyxiation experiments, some or several of the described pathological changes are frequently seen in the brain (Gildea and Cobb, 1930, Tureen, 1936, Weinberger et al, 1940, Windle, 1961) Weinberger et al mention hearing disorders in their cats, but found no pathological changes in the brain stem Windle, however, in his monkeys, after clamping of the umbilical cord, also found hearing deficiencies and affection of the cells in the inferior colliculi Immersion in an atmosphere of nitrogen gas did not result in discernible lesions, possibly because cardiac depression occurred so rapidly that the animals died before any structural changes could manifest themselves This is why the 4 % oxygen was introduced in the present experiments, and as some of the kittens endured severe asphyxiation to the point of cardiac arrest once each day for six

Table I *Statistical evaluation*

Both nuc.	Cell no	Standard deviation	Significance test (t test) t	p	Dors nucl	Cell no	Standard deviation	t	p
Controls	93800	8000			Controls	25100	4 00		
0—10 h	76500	12200	3.6	0.998	0—10 h	16300	4100	4.2	0.999
10—22 h	58300	13700	3.1	0.997	10—22 h	11500	3800	2.7	0.897
22 h—2 d	51700	10600	1.3	0.897	22 h—2 d	11500	4100	—	—
2 d—14 d	52700	7500	—	—	2 d—14 d	8700	4100	—	—

h = hours of asphyxia d = days of asphyxia

days in a row, some cell loss might well have been expected It can only be concluded that kittens are very resistant to a low oxygen atmosphere

Valuable contributions to our knowledge of the effect of asphyxia on nerve cells have in recent years been given by Courville (1952, 1953), Kornyey (1955), Christensen (1956), Cammermeyer (1958) and others None of these authors mention the auditory nuclei particularly, but the laminae III and IV of the cerebral cortex and the Purkinje cells of the cerebellum are evidently especially susceptible to anoxia Courville states that some of the focalization of damage is to be accounted for by the peculiar vascularization of the grey matter in question Some of these focalizing effects, particularly those which occur as a consequence of antenatal or neonatal asphyxia, can be accounted for only on the basis of the action of anoxia on the blood vessels Of special interest to the present study is Courville's explanation of the paradox that the richest vascularized regions are the most vulnerable to anoxia The reason, in his opinion is, that the more dependant upon the amount of blood a given area is for its integrity, the more it will suffer if this supply for any reason is impaired Craigie (1938) observed that the cochlear nuclei, especially the dorsal, belong to the richest vascularized areas of the brain stem It is twice as rich in capillaries as the motor facial nucleus, and more than four times as rich as the pyramidal tract

Kornyey (1955) also states that the anoxia produces vascular disorders, and if these continually or repeatedly appear in the same place, parenchymatous degenerations will follow Cammermeyer stresses the fact that the immature brain is relatively poor in solid material and rich in water This explains why ischaemic conditions in the nervous tissue of the newborn so rapidly result in disintegration of the damaged tissue

Time does not permit to deal with possible sources of error I can only mention that statistical evaluation of the findings has shown that they are valid

In the present investigation, the total sum of the errors are included in the statistical data A cell loss is shown, which primarily takes place in the period 10—22 hous of asphyxiation This cell loss is so extensive, especially for the dorsal cochlear nucleus, that it explains the high tone hearing loss The fact, that no histologically demonstrable degenerations were found in the cochlea of these babies, however, does not quite prove a normal function, as our present methods may not reveal the finer disturbances The present investigation shows, that the normal number of cells in the cochlear nuclei in man is about 100,000 This is about five times as many as there are hair cells in the cochlea, which raises another question What purpose has the complex structure of these nuclei? Time does not permit any detailed description, it may be sufficient to quote Lorente de Nó (1933) who states that each fibre from the cochlea is connected to hundreds of cells in the cochlear nuclei We now know, that the prime function of the cochlea is to turn the incoming sound waves into electrical impulses which are conducted to the brain stem by the bipolar cells of the spiral ganglion The first station capable of an analysis like inhibition or facilitation of the incoming impulses is the cochlear nuclei complex Further research in these 100,000 cells will perhaps give a clue to the understanding of the perception of hearing

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DISCUSSION

Flottorp to Hall

In our (1) investigation of the hearing in patients with athetosis we found that all of them responded positively to one or more of our cochlear tests, — at least in certain frequency ranges We therefore concluded that their hearing loss had a cochlear origin This is in agreement with results from the study of cochlear microphonics as a function of the oxygen (blood) supply to the inner ear

It does not mean, however, that some degeneration of the cochlear nuclei may not occur in addition to a cochlear lesion

Hall s findings certainly demonstrate the existence of such retro cochlear lesions in asphyxic brains of premature humans

Of course there is a great difference between the time of examination, — Hall working with premature babies, a couple of hours after death, we with children (or even adults) old enough to cooperate in rather complicated audiological tests

It is, however, rather tempting to compare Hall s results and his information about the dorsal nuclei being more sensitive to oxygen deprivation than the other parts, — with our (2, 3) last results from the examination of patients with congenital hearing loss in which the only known ethiologic factor is anoxia

In such cases we have found indication of cochlear lesion in ranges below certain frequencies, and not above these limits

If Hall could demonstrate that the dorsal nuclei were responsible for transmitting nerve impulses especially for high pitched sounds, this would supply a very good agreement between his histological data and our audiological findings

(1) *Flottorp, G , Morley, D E*, and *Skatvedt, M* The localization of hearing impairment in athetoids Acta oto Laryng 48, 1957, 404—414

(2) *Flottorp, G* Pathological fatigue in part of the hearing nerve only (Paper presented at the Congress)

(3) *Djupesland, G*, and *Flottorp, G* Correlation between the Metz recruitment test and aural harmonic threshold in various types of hearing impairment (Paper presented at the Congress)

A HUNDRED STAPEDECTOMIES

By

Terje Gundersen

Ears Nose and Throat Department (Head Professor Emil Steen), University of Bergen

Abstract

This article describes the result of the first 100 stapedectomies carried out at the ear nose and throat department of the Bergen University Hospital The method employed was a steel wire fat prothesis *ad modum* Shuknecht Hearing was improved and the bone gap was closed down to 10 decibels or less in 97 cases The hearing remained unaltered in 2 cases One ear became deaf due to infection. In many cases a marked improvement in other frequences

No definite correlation was found between loss of hearing and the invasion of the oto sclerotic bone at the stapes plate Small amounts of blood in cala vestibuli during the operation did not appear to affect hearing improvement

The method used at the Ears, Nose and Throat Department of the University of Bergen for our cases of otosclerosis is stapedectomy with steel wire-fat prosthesis Our technique is the same as that described by Schuknecht et al We have been able to apply this method in all cases admitted for operation, and so far fenestration of the lateral canal has never been necessary

The operation is performed under lokal anaesthetic and only in a few cases has it been necessary to make an incision in the outer part of the external meatus In four cases drill was used on the footplate and in all cases we were able to remove at least 80 % of the plate

Our department was opened in September 1961 The follow up has therefore been rather short, but this is true of all stapedectomy cases This paper presents our first 100 stapedectomies from no 1 to 100

Table I shows the sex groups and Table II the age groups The two oldest patients were 82 and 78 both were operated on successfully

Table III shows preoperative hearing according to Shambaugh This table shows that the occurrence of type C ears is more frequent than types A + B

Table I *Sex groups*

♀	♂	Total
57	43	100

Table II *Age groups*

20—44 years	45—70 years	> 70 years
43	54	3

Table III *Preoperative hearing according to Shambaugh*

A-ears	B ears	C-ears
27	22	51

In group C there were 35 ears with advanced otosclerosis Advanced otosclerosis as herein used refers to clinical otosclerosis in which the bone conduction loss is at least 30 decibels at each of the speech frequencies Four patients had far-

advanced otosclerosis and the bone conduction was not measurable in any of the speech frequencies with a standard audiometer, Peters Spd 5

Pure-tone tests and recorded speech tests were carried out pre-operatively and each patient was given at least two pure-tone tests and one speech recording test The two pure-tone tests were administered preoperatively at least 24 hours apart Postoperatively the hearing was tested two weeks, four weeks and three months after the operation, and afterwards every three months

Table IV shows the postoperative observation period The longest follow up was 18 months in 16 cases

Table IV *Postoperative observation period*

6 months	16 patients
6—12 months	32 —»—
> 12 months	52 —»—

Table V shows the results of surgery The hearing in 97 ears was improved, in 2 ears unchanged, and one ear became deaf These 3 cases will be discussed in more detail later The bone-air gap was closed within 10 decibels or less in all

Table V *Results of stapes surgery in 100 ears*

Improved hearing	Status quo	Deaf
97	2	1
Bone air gap less than 10 db		
97		
Hearing loss not exceeding 20 db in the speech frequencies 500–1000–2000 cps		
40		

97 ears The table also show that 40 ears had a pure tone threshold of 20 decibels or better in the speech frequencis There was therefore greater improvement in some of the ears in group B than might have been expected from the preoperative bone conduction tests In papers dealing with stapedectomies several authors have claimed that the improvement in the bone conduction is evident not only in the 2000 cps, as previously observed in fenestration surgery, but also in other frequencies, especially the bass Our experience is the same The bone conduction is difficult to measure exactly and where the stapes is immobile the cochlear reserve can probably never be measured correctly We used the same audiometer and the same masking technique pre- and postoperatively The alterations in the bone conduction are shown in Fig 1

The diagram is made by plotting in each case the average sum of the following frequencies 500 cps, 1000 cps and 2000 cps On the left are the cases with impaired bone conduction, on the right the cases with improved bone conduction It will be seen that we have recorded improvement in the bone conduction for the average of the speech frequencies up to 60 decibels The usual explanation of this improvement in the bone conduction, i e hidden cochlear reserve, is alteration of the hydrodynamic pattern We can find no better explanation

Fig 2 demonstrates the average improvement of the air counduction at the

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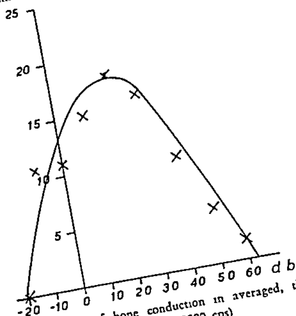


Fig 1 Postoperative alterations of bone conduction in averaged, the speech frequencie (500 — 1000 — 2000 cps)

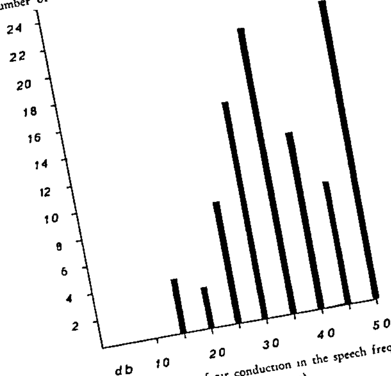
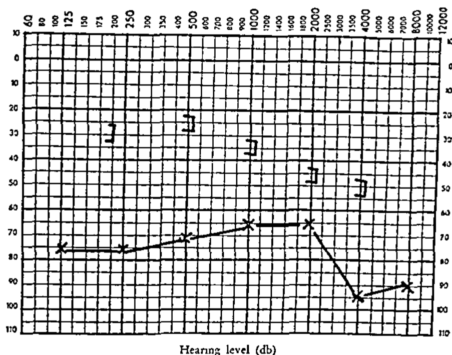


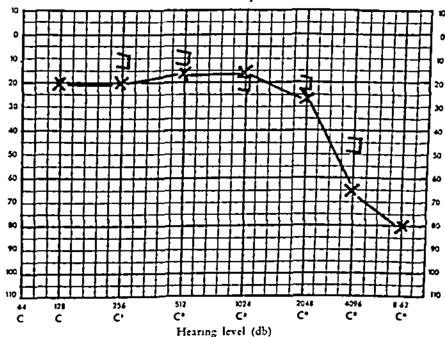
Fig 2 Average improvement of air conduction in the speech frequencies (500 — 1000 — 2000 cps)

Left ear before operation



Hearing level (db)

Left ear after operation



Hearing level (db)

Fig 3

not undergo surgery a second time and we do not know why his hearing was not improved He suffered no postoperative vertigo

The totally deaf ear was due to an infection The patient had an external otitis and should not have been operated on that time He developed purulent labyrinthitis and the ear became stone deaf The ear was re-opened on the sixth day The prosthesis fitted well

One of our patients had a combination of a congenital deformation of the middle ear and otosclerosis The incus was absent and the stapus deformed and immobile due to otosclerotis bone The stapus was removed and replaced by a steel wire-fat prothesis, which in this case was fixed to the neck of the malus Fig 3 shows his audiograms, pre- and postoperatively The patient's other ear was also operated on, and was found to be a normal middle ear with otosclerosis

No one has been able to observe the results of this operation for longer than four years, and a longer period of observation is necessary before it can be finally evaluated Our results nevertheless seem to indicate that stapedectomy is the method of choice in otosclerosis surgery and that fenestration of the lateral canal has very little practical interest The implantation of foreign materials in the middle ear has occasionally been criticized Studies on the tolerance of tantalum and of stainless steel wire reported by Schuknecht, Oleksiuk and Coleman indicate that such wire is completely inert in the middle ear and simply becomes coated with mucosal sheet

Adipose tissue was selected after an experiment by Coleman (1960) in which various types of tissue implanted into the oval window after stapedectomy in cats were examined by sectioning the intact temporal bones In the literature a few cases of sero fibronous labyrinthitis are reported These may be due to slow necrosis of the graft The necrosis probable results from inadequate nutrition of the graft and may appear whether fat graft or vein graft is used (Coleman, 1962)

Our own experiences indicate that small amounts of blood or small pieces of bone fragments in the scale vestibulae do not distort the hearing We found no definite correlation between the extent of the bone air gap and the extent of the oval window pathology

Stapes surgery in advanced otosclerosis is very worth while Even if the patient must continue to use a hearing aid, he will, in most cases, be able to change from a strong body type aid to a less powerful and less cumbersome ear level aid

In none of these cases has the hearing deteriorated since it was tested three months after the operation

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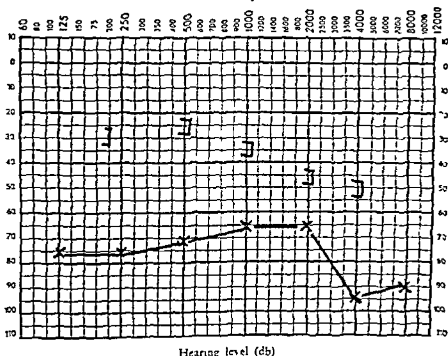
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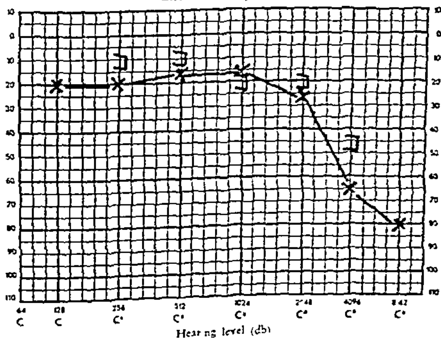
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Left ear before operation.



Hearing level (db)

Left ear after operation.



Hearing level (db)

Fig. 3

FENESTROPLASTY, STAPES SURGERY IN OTOSCLEROSIS

16 mm color film, report in English Length 187 m, duration 17 minutes
Surgery demonstrated by Prof Urpo Siirala Photography Heikki Nieminen

The middle ear is opened through an endaural incision The meatal skin and annulus, the posterior margin of the drum membrane are dissected free from the bony meatus For better exposure of the oval window region the most medial part of the posterior wall of the meatal bone is chiselled away

Part I Stapedectomy is performed after cutting the stapedial tendon and unlocking the incudostapedial joint Fenestra ovalis is sealed with a piece of temporal fascia A "Wing-Grip" polyethylene tube is inserted between the processus lenticularis and the sealed oval window for sound conduction

Part II. The stapedial tendon is cut and the stapedial crura detached from the plate The plate of the stapes is removed, the oval window sealed with a piece of temporal fascia and the posterior crus of the stapes is replaced in the middle of the sealed oval window for sound conduction The skin of the meatus and the drum membrane are replaced, the meatus packed with gauze and the wound sutured

AUDIOLOGICAL EXAMINATIONS OF PATIENTS IN A DANISH HOSPITAL

By

Sonja Filling and *Steen Johnsen*

rom the ear, nose- and throat department of the Copenhagen County Hospital of Glostrup
Head Steen Johnsen[1]

Abstract

n the Copenhagen County and State Hospital of Glostrup (1123 beds) special questionnaires as o the hearing status were filled in for all the 3345 patients entering the hospital during two nonths According to criterias indicating hearing loss 655 patients were picked out for otological udiological examination including pure tone and speech audiometry 288 of those had normal earing and 367 demonstrated different degrees of hearing loss, i e. about 11 % of the total umber had pathological hearing

Of the 367 patients with hearing loss 20 % had a monaural hearing loss, 40 % had a slight, 0 % a medium, and 10 % a severe hearing loss

46 patients already had a hearing aid 37 definitely needed one, and 67 patients were border ne cases for hearing aid

Conclusion 11 % of the total number of patients entering the hospital had some degree of earing loss, about 3 % needed examination with hearing aid 1 % already had a hearing aid

n the Copenhagen County Hospital and the State Hospital of Glostrup, Den nark, with a total of about 1100 beds a series of audiological examinations were erformed in order to demonstrate the frequency of hearing loss in patients ospitalized in an ordinary Danish hospital Furthermore an attempt was made o reveal the need of special audiological examination considering the need of reatment with hearing aid or other forms of audiological therapy

The investigation took place during a period of two months in such a way hat all the 3345 patients entering the hospital during this period filled in the uestionaire demonstrated in Table I

Tab e I

	yes	no
1 Is your hearing normal?	☐	☐
2 Is your hearing normal on both ears	☐	☐
3 Have you ever had discharge from your ears?	☐	☐

220 patients had to be excluded from our material for different reasons Some of them were discharged from the hospital too soon for the examination, and ome were too severely ill to collaborate

Of the remaining 3125 patients 2470 answered the first two questions with a "yes" and the third one with a "no" suggesting that they had never had any ear rouble or hearing disorder So these patients were not further examined

655 patients reported a hearing loss on one or both ears and/or previous

[1] The authors are indebted to the director of the Danish State Hearing Center of Copenhagen H W Ewertsen for practical help in the examinations

draınage from the ears These 655 patıents were thoroughly examıned otologıcally and audıologıcally ın any case ıncludıng pure tone audıometry In cases wıth threshold values poorer than 20 db for more than two of the standard frequencıes speech audıometry was performed wıth an estımatıon of the Threshold of Intellıgıbılıty (TI) and ın some cases also of the Dıscrımınatıon loss

According to these examınatıons 288 patıents turned out to have a normal hearıng and 367 patıents had varyıng degree of hearıng loss, the group wıth hearıng loss thus amountıng to about 11 per cent of the total number of patıents enterıng the hospıtal durıng the perıod of ınvestıgatıon

Table II demonstrates the age- and sex dıstrıbutıon of our materıal

Table II *Age and Sex*

Age	Total number of patıents		Total	Patıents wıth hearıng loss		Total
	Male	Female		Male	Female	
0—14	204	150	354	5	5	10
15—30	236	589	825	16	21	37
31—50	412	707	1119	56	49	105
51—70	288	342	630	75	62	137
>70	81	116	197	37	41	78
	1221	1904	3125	189	178	367

Comparıson wıth the statıstıcal age and sex dıstrıbutıon of the Danısh populatıon *as a whole demonstrates some dısagreement and especıally ın two poınts* 1) A pronounced overweıght of the number of women ın our materıal may be because of the great number of patıents ın the gynecologıcal department and 2) the fact that our materıal comprıses only half of the number of chıldren to be expected from the statıstıcal dıstrıbutıon of the populatıon Thıs may be explaıned partly by the lack of pedıatrıc wards ın the hospıtal

Table II clearly demonstrates that the frequency of hearıng loss ın men ıs much hıgher than ın women

Of the 367 patıents wıth abnormal hearıng 294 were sufferıng from bınaural hearıng loss, and 73 patıents had a monaural hearıng loss Sınce as a rule mon aural hearıng loss does not claım audıologıcal therapy these 73 patıents shall not be mentıoned further

But as to the 294 patıents wıth bınaural hearıng loss an estımatıon ıs made regardıng the degree and type of hearıng loss as shown ın Table III

Table III *Degree and Type of hearıng loss ın the bılateral cases*

	Total number of patıents	Percept type	Conduct type	Mıxed type
Slıght	207	135	30	42
Medıum	75	39	16	20
Severe	12	5	0	7
	294	179	46	69

The hearing loss is classified as slight if TI is 30 db or better TI between 31—60 db is described as a medium severe hearing loss, and TI of 61 db or poorer as severe hearing loss

According to this classification 87 patients or a little less than 3 per cent of the total number of patients entering the hospital during the period of investigation were suffering from medium or severe hearing loss on both ears Slight degree of hearing loss was found in about 6 5 per cent

Perceptive type of hearing loss was by far the most common in our material

Our recommendation of procuring of a hearing aid was made according to the criteria generally practiced in the audiological clinical work According to this our binaurally hard of hearing patients may be subdivided in the following 4 groups

1) 46 patients were already on beforehand using a hearing aid 2/3 of these hearing aids were given free to the patients from the Danish State Hearing Centers, 1/3 were provided privately by the patients from the hearing aid dealers

2) In 37 patients there was a definite need for hearing aid therapy These patients were referred to a State Hearing Center

3) 66 patients were suffering from a hearing loss of such (slight) degree that they were borderline cases regarding use of hearing aid Only fitting of hearing aid or maybe using a hearing aid for a test period might be of help to these patients

4) In 145 patients the hearing loss was so slight that hearing aid was absolutely not in question

As a conclusion of our investigation we found that about 11 per cent of the total number of patients entering the hospital had some degree of hearing loss 1 5 per cent of the patients were already on beforehand wearing a hearing aid 1 2 per cent of the patients were definitely in need of a hearing aid and 2 3 per cent of the patients had a hearing loss placing them as borderline cases as to the indication of hearing aid.

So in the hospital where this investigation took place with about 20,000 patients entering the hospital a year a little more than 600 patients should have a so far not fulfilled requirement of audiological examination 200 of these patients having a definite need of hearing aid therapy

NINE YEARS EXAMINATION OF THE HEARING IN SCHOOL CHILDREN IN NORTH TRØNDELAG

By

H F Fabritius

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Abstract

A survey is given of the examination of the hearing in schoolchildren in North Trøndelag carried out through nine years (about 30 000 children) Special reference is given to about 6 000 of the children, observed through the whole schooltime of seven years

I have previously talked about the examinations of hearing amongst school children in northern Trøndelag province, and I shall therefore not repeat my self I shall only briefly mention that we examine annually all the children in the 1st, 4th and 7th classes with the aid of screening examinations followed by specialist examinations The screening examinations have, to a large extent, been made by health visitors who are occupied with the health and hygiene work in the various medical zones The specialist examinations have mainly been done by me — and most of the hospital treatment has been undertaken at Namdal Hospital I have therefore had plenty of opportunity to follow the whole work and gather a deal of experience

After having been occupied with these examinations rutinely for 9 years, I have felt it a duty at this point to look back a little and state some of the work up to now — and to mention some of the experience gained — and lastly to say a little about the audiological team work

Amongst those things to which I wanted an answer was the frequency of impaired hearing in a larger school-child material and what was the cause of this impairment There are now 3 year batches of children who have been followed through all their 7 years at school, and there is a particular interest bound to this homogeneous material I wanted to know with what degree of accuracy the screening was done by us And lastly I wanted to know the frequency of greatly impaired hearing and where we, within a certain period, find all these children with greatly impaired hearing when they have reached school age

First I shall give a review of the numbers with which we have to do during these years (Table I)

We see here that a little over 51,000 examinations have been made in the course of the first 8 years, but that it concerns about 29,000 children because some have only been examined once, some twice, and some three times

The numbers within each annual should actually have corresponded better

than they do in this review, but in my latitudes things like the weather, road conditions and communication difficulties play their part, but I can mention that those who were not examined the one year were taken the next.

Table I

	Classes			
	1st	4th	7th	Sum
1954	2220	1899	1684	5 803
1955	2347	2172	1796	6 315
1956	2060	2240	1959	6 259
1957	2202	2239	2072	6 513
1958	2205	2170	2150	6 525
1959	2232	2120	2349	6 701
1960	2178	2114	2154	6 446
1961	2153	2189	2287	6 629
	Sum of examinations			51 191

Examined in 1st or 7th class	12 002
» » 1st & 4th or 4th & 7th class	12 852
» » 1st, 4th and 7th class	4 324
Approximate number of children	29 178

The next table (Table II) shows what percentage is, on an average, called in (6 5 %), what percentage comes in for examination (97 %) and the average degree of impaired hearing (3 4 %)

Table III shows that on an average there are 8—9 % who are mistakenly

Table II

	54/55	55/56	56/57	57/58	58/59	59/60	60/61	61/62	Total
Number of examinations	5803	6315	6259	6513	6525	6701	6446	6629	*51 191*
Percentage called in for examination	7 8	2 7	6 4	4 6	6 4	6 1	9 3	8 5	Average percentage *6.5*
Percentage that appeared for examination	97 7	97 0	95 7	96 2	97 5	98 5	97 6	93 6	*97 0*
Percentage of impaired hearing	4 0	1 7	2 0	2 5	2.8	4 1	5 3	4 9	*3 4*

Table VI

Diagnosis	Classes					
	1st		4th		7th	
	Number	(%)	Number	(%)	Number	(%)
Otosalpingitis	73	(55)	56	(32)	49	(18)
Otitis media acuta	0		1		1	
Otitis med. supp chron	5		3		2	
Otitis med chron operata	3		3		5	
Sequelae otitidis	14	(11)	51	(30)	131	(47)
Hypacusis conductiva e causa ignota	1		1		1	
Malformatio auris mediae	1		1		1	
Hypacusis perceptiva	21	(16)	38	(22)	60	(22)
Hypacusis percept congenita	6		6		5	
Hypacusis acustotraumatica	3	(2)	7	(4)	13	(5)
Anacusis monauralis	5		6		7	
Sum	132		173		275	
Total number of children 5947						
Impaired hearing in per cent		2 2%		2 9%		4 6%

pupil who has this diagnosis in all three classes Of the 73 in the first class there are 49 who become normal and remain so 5 have otosalpingitis in the 4th class too, and 19 develop some consequental condition 5 of the 56 otosalpingitises in the fourth class come from the first class 51 are children with normal hearing in the first class There are 41 of these 56 children who have become normal by the time they reached the seventh class, amongst them all those 5 who had otosalpingitis both in the first and the fourth classes One had otosalpingitis both in the fourth and seventh class, and 14 developed consequental conditions Of the 49 who had otosalpingitis in the seventh class there is one who had otosalpingitis in the first class, one who had otosalpingitis in the fourth class and 47 who were previously normal

Table VII

	Classes		
	1st	4th	7th
	73	Otosalpingitis 56	49
Normal Otosalpingitis Sequelae otitidis	73 → 49 73 → 5 73 → 19	51 → 56 → 41 5 → 56 → 1 56 → 14	47 → 49 2 → 49
	14	Sequelae otitidis 51	131
Normal Otosalpingitis Seq... itidis Oti	14 → 13 14 → 1	19 → 51 → 1 19 → 51 13 → 51 → 50	67 → 131 14 → 131 50 → 131

If we so consider the sequelae of otitis media we find here 14 in the first class and of these 13 who have the same diagnosis in the fourth class — and one who is given the diagnosis chronic otitis In the fourth class there are 51 sequelae, 19 of these were previously normal, 19 had otosalpingitis in the first class and 13 had the same diagnosis in the first and the fourth class One of these became normal again after a myringoplasty And so we have the 131 in the seventh class of which 50 come from sequelae in the fourth class 14 from otosalpingitises in the fourth class and 67 who had previously had normal hearing I think it is interesting to watch this development both from an otological point of view and with regard to the prognosis of hearing

Concerning the latter one can say unconditionally that the prognosis for otosalpingitis is good — and the same is mainly true for the sequelae

In only five cases amongst these sequelae patients does a chronic condition develop which one could characterize as an adhesive process

We have good anamnesic information on the school children with impaired hearing With regard to the children with sequelae, it appears that all of them had had ear diseases before they began school Some of these, of course, have had ear disease during school years, but according to my findings, there is a series of children who had ear disease while they were quite tiny and who, to begin with, were registered as having normal hearing, but who gradually developed a registerable hearing loss during school years

The practical consequence of this must be that ear diseases during pre-school age must be taken as seriously as possible, that we realize that we are dealing with a sense organ and that audiometary hearing examinations must be part of the routine treatment

In Table VI we see that there are in the seventh class about three times as many children with neurogenic impairment of hearing as there are in the first class Here they are naturally the same children who appear again, but with a little increase each year The hearing reductions which come in addition are partly so called high tone-losses which have different causes, but in a great many cases one can suspect the gradual onset of neurogenic deafness with some suggestion of a u shaped audiogram One gets the impression that already at this point changes due to age are beginning to make themselves felt.

On the prognosis of hearing I would just like to mention that amongst those with a congenital neurogenic deafness, there was only one who had a moderate but clear progression of his condition during school years The others remained stationary Amongst the acoustic traumae all in the first and the fourth class have an increase in their dip of 20 db or more during the period of observation But there is no increase in the width of the dip Whether or not this increase has come unaided or, because the child has exposed himself to further acoustic traumae is not possible to say

I have inquired as to whether there is any difference in the frequency of hearing loss between boys and girls, but I find here no difference at all — the acoustic traumae excepted I have also inquired about the difference in frequency of

deafness or ear diseases between the coast district and the inland, but neither have I found any differences here This may though in the meantime be due firstly, to the material at my disposition being too small, and secondly because there is no great climatic difference between the easterly and westerly parts of the province since it is so narrow

One can gain some impression of the involvment of the pharynx tonsil by observing those diagnoses in which it is associated (Table VIII)

We see here that one finds an enlarged adenoid primarily in connection to catarrhal or inflammatory changes in the ear — and with otosalpingitis as a good number one This is the same as other inquirers have found

Of 107 who had their adenoids removed and who have been re evaluated after an observation period of either 3 or 7 years, there were 62 whose hearing improved after the operation, 43 remained unchanged and 2 whose hearing became worse The latter, however, should not be attributed to the adenoidectomy It is here without doubt the ear disease as such which is the cause of the progression

In order better to judge our screening audiometry I have taken from the whole material 153 children with neurogenically impaired hearing, of those in whom one could suppose the degree of deafness to remain constant and where one has several examinations and check-ups to go by Amongst those I have found 22 that must be counted amongst the mistakenly registered — in other words one must reckon on about 14 per cent false registerings This in the meantime sounds rather a large percentage, but when one considers how the registerings have usually been undertaken on children whom one does not know, sometimes in un satisfactory surroundings and often with too little time at one's disposal — the result is perhaps not surprising In an unspecified selection of such cases we discovered that our trained audiometry nurse made just as many mistakes as the health visitors who had less training in this work

Table VIII *The influence of the pharynx tonsil*

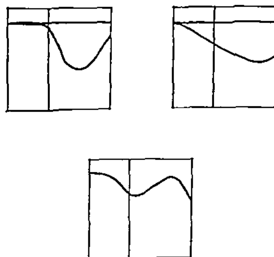
Diagnosis	Classes			
	1st	4th	7th	
	Number	Number	Number	
Otosalpingitis	73	56	49	
hereof with vegetationes adenoides	60	15	4	i e 46% with vegetationes adenoides
Sequelae otitidis	14	51	131	
hereof with vegetationes adenoides	13	14	8	i e 27% with vegetationes adenoides
Otitis mediae chron ca	5	3	2	
hereof with vegetationes adenoides	3	0	0	i e 30% with vegetationes adenoides
Hypacusis neurogenes	21	38	60	
hereof with vegetationes adenoides	8	5	0	i e 15% with vegetationes adenoides

The figure 1 show some typical examples in which at first examination the hearing was registered as normal on both ears Usually only one ear is mistakenly registered, but occasionally both

But I am so presumptuous as to suppose that we in Trøndelag on the whole do not make any more mistakes than most other people in this branch around the world The practical consequences of these false registerings should, in my opinion, be that one undertook examinations at shorter intervals, especially in the lower classes

Fig 1 Evaluation of the correctness of the screening audiometry
In 153 cases of perceptive impaired hearing examined twice or more, the registration turned out to be incorrect in 22 cases — i e *14 %*

Examples



In order to get some idea of the frequency of greatly impaired hearing, by which I mean of more than 30 db on the best ear, I have gone through six successive school classes I have not taken more on account of what I have said about false registerings and I only wanted those children who had been through at least two examinations (Table IX)

T a b l e IX *Survey of greatly impaired hearing in comparison to the number of live births during six years*

Number of children born in		Impaired hearing > 30 db better ear	Per cent
1947	2 200	3	0 14
1948	2 409	4	0 16
1949	2 303	5	0 20
1950	2 315	3	0 13
1951	2 325	6	0 26
1952	2 445	5	0 20
Sum	13 997	26	0 18

Number of children entering school 1954–1959 14 063

Here were 13 997 live births in northern Trondelag in the six years from 1947 to 1952 and of these 26 had greatly impaired hearing, that is to say 0 18 per cent

It is perhaps more practical to see these figures in comparison to the number of children that began school seven years later That number was 14 063 — which shows a little immigration to the province — but since the figures are so close to each other the percentage is the same

Table X *Causes of greatly impaired (better ear > 30 db)*

Hereditary cause	–
Maternal rubella	1
Multiple defects	1
Erythroblastosis fetalis	1
Birth injuries	3
Cerebral palsy	3
Head injuries	1
Diseases of the ear	4
Unknown cause	5
Sum	26

The causes of impaired hearing appears from the table X There were only 4 where the cause was ear disease The rest were neurogenic deafnesses

Where we do find these 26 children when they have reached school age appears from the following table XI, and we find the average loss of hearing in db beside the number

Half of the children we find in normal school One is dead due to a traffic accident, probably as a result of her deafness One has left the province One is at home after having been on trial both at the school for the deaf and the school for mentally deficient And the rest go to special schools

What interest us most in this table are those 13 in normal school Even though one can help them to a certain degree with hearing aids, this alone is not enough — and with the lack of assistant teaching still to be found in Norway, it is obvious that these children do not get all the benefit of schooling that they should get

Table XI *Where the 26 children with greatly impaired hearing are found*

	Number	Average hearing impairment in db
Normal school	13	46 db
School for the partially deaf	4	75 »
School for the deaf	1	96 »
School for educationally subnormal	3	35 »
School for brain injured children	1	56 »
Home for cerebral palsy	1	58 »
At home	1	90 »
Moved out of the county	1	47 »
Dead (in traffic accident)	1	50 »
Sum	26	

The results of this examination shows us that in our elementary schools in Norway to-day we have a group of children with greatly impaired hearing who do not receive the help they should — either in the form of assisted teaching in normal school or by admission to schools for the hard of hearing Most of these children will not be found before systematic examinations of the hearing of all the country's schoolchildren is instituted

In the course of the nine years in which we have been doing these school child examinations — and to a large extent because of them — there has gradually developed a team-work between institutions and persons which has been very useful

The first was a kindergarten in Trondheim for children with greatly impaired hearing The next was our first and as yet only school for hard of hearing children, just a little way north of Trondheim, and I have had the pleasure of being connected to this school

Two years ago a travelling teacher or parent's guide was appointed at this school, and he did an invaluable job in the form of guidance in homes where there were infants with hearing injuries — and in the same manner in both schools and homes where there were school children with impaired hearing

In the course of the last year we are able to control hearing aids and an electro technician has been appointed This has also been of great importance

The examination of school children has lead to an extensive team-work with district practitioners and on account of the combined interests of these practitioners and that of the province's medical supervisor, screening audiometers have been acquired in all the medical districts Lastly I would like to mention that we have met with close co operation from all the respective communities, schools and teachers In this manner we have succeeded in a little way with our audiological team-work which we hope to continue in the future

1

DISCUSSION

Nielsen to Fabritius

During the last 22 years a hearing conservation program has been carried out within the public school system in Esbjerg All schoolchildren of all ages have been tested yearly

When this program was started in 1940 we stated our hypothesis that it would be of prophylactic value and serve to conserve the hearing of the children of this school system We also anticipated that a program of identification audiometry within the public schools would be the basis for a hearing conservation program for the entire population

Due to the fact that Dr Fabritius has anounced a discussion of the hearing conservation program in Nord Trøndelag we intend to discuss the extent and degree of the success of our program

It should be understood that a question like this could not be answered satisfactorily until the program had been working for a certain length of time or until the material studied would be of a certain magnitude

During the last 22 years 60,618 screening tests have been performed using the group screening test devised by us in 1940 The group auditory test was designed to identify children with actual hearing losses or with suspected hearing losses The number given above does not include any of the individual hearing tests performed after screening in order to verify the presence of actual hearing loss

From the statistic material we have extracted one factor only, namely the percentage of children with such binaural hearing losses that special education or habilitation such as in the form of amplification, lipreading training, auditory training, education in a class for hard of hearing children, etc was considered necessary

We shall consider the variation of this percentage as a directive which will give us certain information, although only of relative value, about the actual hearing status of the entire school population at a certain time

During the last years a certain degree of surprise has been ventilated as to the obviously low percentage of severely handicapped children which is given in the annual reports of our school system

On such occasions we have always referred to the effect of a hearing conservation program when combined with medical treatment

Before we shall venture to support this statement by numbers it should be noted that source of reference may be found in the annual reports of the public school system in Esbjerg These reports have been published throughout the years

In the annual reports one may also find specific reference to the diagnosis of otolaryngological diseases which were found in connection with hearing losses, a list which will specify the medical prophylactic side of the hearing conservation program

I shall not here give reference to this side of our program and I shall sum up with the following

During 1940 4247 children were tested using the whispered voice test 0 7 % of these children were found to be in need of special habilitative measure due to severe hearing losses

After this group audiometric testing was started and as expected we found an increase in this percentage from 0 7 to 0 9 % during the first years

The effect of the hearing conservation program was not yet to be seen No actual school for hard of hearing children had yet been established in which one could have each case under constant and effective control or where the treatment carried out by the school nurse or by the school otologist could be followed up

It was not until 1953 that the conservation program in the form of a school for the hard of hearing was started in line with the regulations for schools for the hard of hearing in Denmark

During the following period until 1962 we find a noticeable decrease in the percentage of children with severe hearing problems the decrease is from an average of 0 9 to an average of 0 1 %

These results mean that after 22 years of work with the Esbjerg system we may calculate that 0.1 % of all children need special treatment of some sort due to their hearing problems

It may also be expressed in the following way The program used in Esbjerg has shown to be of considerable effect as a hearing conservation program to that the number of children with severe hearing losses has decreased by ten times as compared to the former occurrence of hearing losses during the period when there did not exist a hearing conservation program in our school system

In Esbjerg we hade considered the above results to be very satisfactory and we believe to be able to answer the question concerning what is of importance in a hearing conservation program for school children

First of all the screening test used must be of such a design that it will sort out even the smallest hearing losses in order that these may be treated as early as possible

However, this is not enough Afterwards one must be able to effectively control if treatment takes place and if it is of positive effect in each case

The actual results depend upon whether it is possible to arrange for such a control system within the school system in question

With regard to this Esbjerg has the best possible facilities Distances are such that it is easy to bring each pupil in for control at the office of the school otologist or for further auditory testing

Transport may take place by bus when a group is assigned for testing or the individual child may arrive by bicycle or on foot

The Esbjerg system functions so that the otologist is present from the very beginning of the program and we consider this to be of great advantage as compared to the way programs are set up in other places I have been informed that in some places in Norway about a month will pass *from the time of the* initial auditory testing until the examination by the otologist takes place due to the enormous distances in this country With such an interval there is a risk that very important factors will be overlooked

EXAMINATION OF HEARING IN ALCOHOLICS

By

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Abstract

90 alcoholics were examined at Bjørnebekk kursted, Ås, Norway 5 patients had chronic otitis media, 2 had been treated with streptomycin in major doses, and these were not included in the survey Among the remaining 83 patients 14 were found to have hearing losses, 9 of those had been exposed to noise and 2 to detonation injury It is discussed, whether alcohol adds to the susceptibility of the organ of Corti and so makes it more vulnerable to acoustic trauma, or whether special occupations in the present group of patients might account for an incidence of occupational deafness higher than that which is found in the average population There was no case of hearing loss to be explained as due to the effect of alcohol only

Several authors, even of textbooks, state that alcohol is a poison attacking the inner ear (the organ of Corti) and/or the acoustic nerve Thus in his textbook of ear, nose and throat diseases Morrison (12) states that "Alcohol acts to cause a degeneration of the hair cells of Corti's organ and produces nerve deafness" Hallowell Davis (5) in his textbook Hearing and Deafness (1960) hints that toxic injuries can not be distinguished from noise injury Both of them give a nerve deafness, which is due to a degeneration of these sensor cells of the organ of Corti and the nerve fibres We are unable by hearing tests or other tests to distinguish between the two etiological factors, both are typical nerve deafness Davis further notes, that we do not know why one individual is more susceptible than another when exposed to toxic agents (or noise injury) In Nordisk Lærebog i Oto rhino laryngologi Lennart Holmgren (11) states in his chapter on audiology "It is not quite known how important regular use or abuse of such poisons or pharmaca (alcohol, tobacco, salicylates etc) are to the hearing In cases of abuse serious acoustics neuritis has certainly been caused"

As far as can be ascertained no recent investigations exist concerning the influence of alcohol on the hearing Nakamura in an investigation from about 1920 found that both ethyl and methyl alcohol damaged the hearing organ In his opinion it was usually the sensory cells, the ganglion cells, and the cochlear nerve fibres that had suffered The changes were of a degenerative atrofic nature The concept that alcohol is toxic to the hearing organ is also supported by the fact that in alcoholics one quite often finds polyneuritis, possibly because of a deficiency of vitamin B — The influence of *acute* alcohol intoxication on the *vestibular organ* should be well known, and has been exactly established experimentally through electronystagmography by Ashan and Goldberg (8)

Material and investigation

In order to investigate a possible relation between alcohol and nerve deafness, 92 patients were examined during their treatment at Bjørnebekk Kursted, Ås, Norway, which is a public sanatorium for male alcoholics The sanatorium has

on an average 60 patients under treatment In the course of one year about 300 patients are treated

The investigations took place at Bjørnebekk Kursted in the autumn of 1962 All patients were subjected to a complete ear, nose and throat examination An exact history was taken, including family history The patients were particularly closely questioned about ear, nose and throat diseases, and whether possibly toxic agents had been used such as streptomycin quinine, acetylquinine etc They were questioned regarding exposure to noise, smoking habits head injuries, commotio cerebri, previous meningitis/encephalitis mumps and syphilis All patients underwent a general examination including neurological survey, carried out by the physicians at Bjørnebekk Sanatorium

On all patients a pure-tone audiogram and a tone-decay test at the frequencies 500, 2000 and 4000 cps on both ears were recorded

W H O defines alcoholism as follows

"Alcoholics are those excessive drinkers, whose dependence upon alcohol has attained such a degree that it shows a noticeable mental disturbance or an interference with their bodily and mental health their interpersonal relations, and their smooth social and economic functioning or who show the prodromal signs of such development"

Of 92 patients examined at Bjornebekk Sanatorium 90 were diagnosed as alcoholics

4 patients with unilateral chronic otitis and one patient with bilateral chronic otitis were not included in this survey The same applies to two patients who had been treated with streptomycin in major doses One of those two patients had a pure tone threshold audiogram showing a bilateral nerve deafness in the treble from and including 6000 cps, whereas the other one had only a moderate nerve deafness on the left side

There were no patients with otosclerosis or congenital hearing loss in the material

The remaining 83 patients in whom a possible hearing loss might conceivably be due to an excessive consumption of alcohol are distributed according to age as recorded in Table I

Table I *The age of the examined alcoholics*

20 years and younger	3	patients
21 30 years	18	»
31–40 years	36	»
41 50 years	15	»
51 60 years	10	»
Over 60 years	1	»

The youngest patient examined was 17 years old and the oldest one was 66 years old The average age was 36½ years

A patient with a possibly psychogenic hearing loss was included in this survey This patient was a 33 years old man, who on the first examination was found to have a bilateral nerve deafness of about 60 decibels He was later seen at the out patients department at Ullevål Hospital, the ear, nose and throat department,

where he underwent a complete audiological and neurological examination He was now found to have a normal audiogram and a normal neurological status, and so he was thought to have a psychogenic hearing loss

The age at the onset of alcoholism is recorded in Table II In about 2/3 of the patients the intake of alcohol has started after 20 years of age — 19 patients have mainly consumed beer, 21 patients mainly spirits, and the remaining 43 patients reported the intake of both beer and spirits

Table II *Shows at which age the misuse of alcohol had become chronic*

The alcoholism was chronic in the age of	Number of patients
15–20 years	27
21 25 years	25
26–30 years	17
31–40 years	11
41 50 years	3

The duration of alcoholism is recorded in Table III Almost 75 % had been addicted to alcohol for more than five years

Table III *Shows the duration of alcoholism*

The duration of alcoholism	Number of patients
Less than 2 years	1
2– 5 years	17
6–10 years	27
11 20 years	28
More than 20 years	10

Result of the examination

14 of 83 patients were found to have an abnormal audiogram 69 patients had normal hearing

Table IV shows the distribution of patients with normal and abnormal hearing according to the duration of the abuse of alcohol

Table IV *The table shows the distribution of patients with normal and abnormal hearing according to the duration of the abuse of alcohol Patients with acoustic traumas are recorded separately*

The duration of alcoholism	Pathological audiograms		Normal audiograms		In all
	In all	Of those exposed to noise	In all	Of those who worked in noise	
Less than 2 years	0	0	1	1	1
2– 5 years	3	1	14	7	17
6–10 years	6	6	21	10	27
11 20 years	5	4	23	9	28
More than 20 years	0	0	10	4	10
In all	14	11	69	31	83

A striking number of patients reported of occupational noise exposure This applied to 31 of 69 patients with normal hearing and to 9 of 14 patients with hearing losses Thus 40 of 83 patients gave evidence of having worked in noisy surroundings for shorter or longer periods

11 of 14 patients with hearing losses had audiograms compatible with noise injuries 9 of them reported of work at a considerable noise level (mentioned above) and 2 of blast injuries

The duration and the character of the exposure to noise in the 11 persons with hearing losses were

1 (pat no 7)	Pilot for 6 years
2 (pat no 12)	Worked with air hammer for 3 months
3 (pat no 25)	8 years in engine room
4 (pat no 35)	8 years as a whale gunner
5 (pat no 46)	2 years in a mechanical workshop
6 (pat no 49)	12—13 years in engine room
7 (pat no 59)	Working as tank welder for 3 years
8 (pat no 63)	12 years as engineer, dieselmotor
9 (pat no 90)	35 years as tin smith
10 (pat no 9)	Hypacusis neurogenis sin, about 70 decibels hearing loss Cracker exploded close to the left ear when the patient was 10 years old Afterwards pronounced hearing loss on the same ear
11 (pat no 66)	Hypacusis neurogenis sin, with a dip a 4000 cps (45 decibels) The patient had been a keen competition rifle marksman

A further analysis of the material shows among the 31 alcoholics with normal audiograms, but with a history of exposure to noise, the following distribution according to the duration of the abuse of alcohol (see Table IV) Among the 14 in group 2 who had been alcoholics for 2—5 years, 7 patients had been exposed to noise In the next group one finds that 10 of 21 patients had worked under noisy conditions Among those who had been drinking for 11—20 years a positive history was found in 9 out of 23 patients and in the last group 4 out of 10 patients

In 11 patients with impaired hearing both the information regarding the character of the noise and the configuration of the audiogram suggested that the observed hearing loss might be due to acoustic trauma

Thus there is a strikingly greater number of hearing losses due to acoustic trauma in these material (13 %) than that which is known from the average population Bentzen and Jelnes (3) in a population of 5000 persons found 33 with acoustic traumatic hearing losses, i e 0 66 % For a material from a hearing clinic the acoustic traumas constituted 5 4 % (Årsberetning, Statens Horecentral, Århus, 1961) (2)

This accumulation of acustotraumatic hearing losses in patients suffering from chronic alcoholism may support the assumption that long standing alcoholism

might add to the suspectibility ('sensitivity') of the organ of Corti, which thus becomes more vulnerable to noise

In order to investigate this possibility both those with normal hearing and those with impaired hearing were recorded according to the duration of the alcoholism (Table IV)

When the material is more closely examined such a theory of increased susceptibility appears little likely According to such a theory one would expect the number of acustotraumatic hearing losses to increase with the duration of the alcohol consumption This is not found When recorded in groups according to the duration of the alcohol consumption one will find the same relative distribution as in alcoholics with normal hearing, and without any accumulation in those groups with long standing abuse of alcohol (Table IV) Thus one is found in the group which had been drinking for more than 20 years Among the alcoholics with normal hearing, on the other hand, one finds in the same group 4 of 10 patients who had been working in noisy surroundings (from 4 to 15 years in engine/mechanical workshop) without having sustained any damage of hearing in spite of the fact that they have been alcoholics for more than 20 years

Perhaps it is not the duration of the abuse of alcohol, but the whole quantity of consumed alcohol that is of importance for the "susceptibility" of the organ of Corti This is a very interesting problem However, it is very difficult to get an exact specification from the alcoholic himself of the alcohol consume An answer to this problem can therefore not be given

4 patients had a history of polyneuritis, see Table V

Table V *In a material of 83 alcoholics 3 patients were found with temporary symptoms of polyneuritis One patient had persistent symptoms of a chronic polyneuritis*

Age	Symptoms of polyneuritis	Alcoholic for	Consumed	Hearing	Neurological status at the time of the examination
40 years	Temporary symptoms in 1957 Treated in a hospital	20 years	Beer and spirits	Normal	Normal
34 years	Twice temporary symptoms 1955 and 1962 The first time treated at the State Hospital Oslo	12 years	Spirits	Normal	Normal
41 years	From 1949 he had hyposensibility of the 4th and 5th fingers of the left hand Muscle atrophy	13 years	Beer and spirits	See audiogram and text	Hyposensibility of 4th and 5th fingers Considerable atrophy of hypothenar and interossei Otherwise normal status
55 years	Temporary symptoms in 1949 Treated in a hospital	30 years	Spirits	Normal	Normal

From Table V it is evident that in 3 of the patients the symptoms of polyneuritis had been intermittent, and absent at the time of examination The neurological examination was negative All 3 had normal hearing One patient had

persistent symptoms of a chronic polyneuritis in the ulnar fingers of the left hand, and this was confirmed at the neurological examination. The neurological status in this patient was otherwise negative. He had worked for 8 years in the engine-room onboard ships. At the audiometry test he was found to have a bilateral dip of 30 to 35 decibels at 4000 cps. The patient is included among the 11 patients with hearing loss due to acoustic trauma (vide audiogram, Fig. 1).

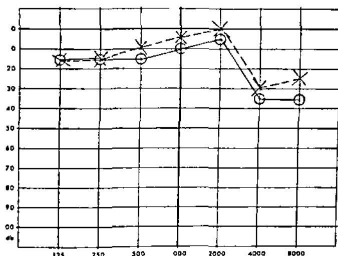


Fig. 1

Two patients had been addicted to spirits and two to beer and spirits.

Polyneuritis in alcoholics is supposed to be due to a lack of aneurin. It has been established that the symptoms of polyneuritis can disappear in spite of unrestricted consumption of alcohol, if adequate amounts of aneurin are supplied.

Accordingly it was impossible even in alcoholics who had displayed symptoms of polyneuritis to establish any hearing loss of which alcohol could be a direct cause.

According to this material alcoholism is found very frequently in sailors. Thus about 45 % of those examined stated that they were, or for some time had been, sailors. Employees in industry or workshops were often found in the present survey. These various categories often work in noisy surroundings (machinery). In my opinion this may be why hearing loss due to acoustic trauma is so often found in alcoholics. This is compatible with the findings at previous examinations of hearing in engine-room men, where hearing loss due to acoustic trauma was found much more frequently than in the average population (personal communication — Ole Bentzen).

The reason why so many authors state that chronic alcoholism can cause nerve deafness may be the observation that nerve deafness is often found in alcoholics. Thus alcohol has been considered the cause possibly without due consideration to the fact that among alcoholics one will more frequently find people who have worked under noisy conditions than in a corresponding normal group of people.

3 patients with hearing losses of doubtful ethiology remain to be described

Patient number 24· 36 years old man He had been an alcoholic for 16 years When 15 years old commotio cerebri with otorrhoe on the left side Worked for 15 years in the engine-room onboard ships The audiogram shows on the left ear a moderate hearing loss in the treble from and including 1000 cps, most pronounced at 40000 cps (vide audiogram, Fig 2) According to the audiogram the

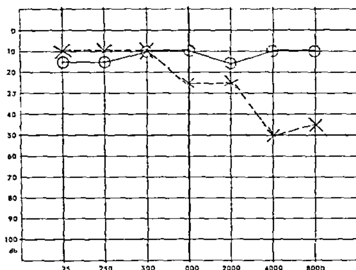


Fig 2

impaired hearing could be explained as due to previous otitis (fractura cranii? with complicating otitis?) and exposure to noise for 15 years The monolateral hearing loss contradicts alcoholic intoxication

Patient number 27 A 45 years old man Alcoholic from the age of 41 A sailor from 20 years of age, now captain When 22 years old he had malaria, treated with quinine, and at this time a bilateral tinnitus started No definite information regarding noise The audiogram shows bilateral asymmetrical nerve deafness, most pronounced on the left ear (vide audiogram, Fig 3) The asymmetrical hearing loss suggests the existence of not only the influence of quinine or alcohol, but more probable of noise

Patient number 28 60 years old Since the age of 56 been an alcoholic Since the age of 53 bilateral moderate deafness of unknown cause Worked in a machine-room for 6 months The audiogram shows a moderate decline in the higher frequencies, most marked at 4000 cps (vide audiogram, Fig 4) The audio gram suggests a nerve deafness aggravated by noise? Considering the age of the patient and the short period he had been drinking (4 years) the most probable explanation on his impaired hearing is an incipient presbyacusis, aggravated by noise Any other ethiology is difficult to accept and under no circumstances can the audiogram be said to confirm diagnosis of alcohol intoxication

In the material of 82 alcoholics it has not been possible definitely to etablish any hearing loss which can be due to the effects of alcohol on the organ of

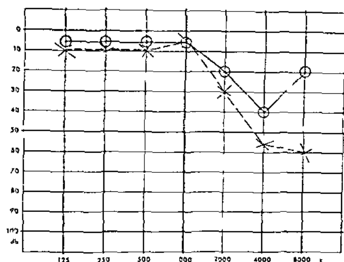


Fig 3

Corti or the 8th cranial nerve, not even in patients who had consumed the largest amounts of alcohol for a number of years Nor has any support to the theory of increased susceptibility to noise of the organ of Corti been found

Since the material only comprises 83 patients, one should not draw too definite conclusions The investigation has failed to confirm the previous assumption that hearing loss may be due to consumption of alcohol

The reason why one failed to find in alcoholics an impaired hearing, that could be attributed to the influence of alcohol on the organ of Corti or the 8th cranial nerve, may be that diets have been improved, with the result that the intake of vitamin B even in alcoholics is sufficient Against this the 4 patients in the material who had displayed symptoms of polyneuritis without changes in the audiogram are to be posed

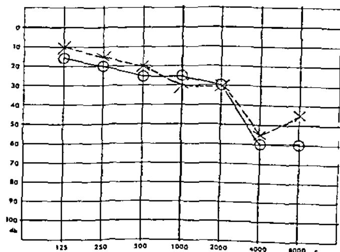


Fig 4

Carhart (4) and Sørensen (13) found marked tone decay in patients with affection of the 8th cranial nerve (where recruitment is uncharacteristic) All 83 patients were examined for tone decay at the frequencies 500, 2000, and 4000 cps All had normal tone decay tests

Finally I should like to mention that in my notes I have recorded that in 80 of 92 patients posterior rhinoscopy and laryngoscopy were very easy to perform This is a much higher percentage than in a corresponding normal population The explanation in all probability is to be found in a hypesthesia of the mucous membrane of the throat due to the long standing consumption of alcohol

CONCLUSION

Among 83 patients with chronic alcoholism of an average duration of 11 years 14 persons were found to have nerve deafness 9 patients with symmetric hearing losses had definitely been exposed to noise at work, in 2 cases monolateral dips at 4000 cps were found, one as the result of a shot, the other after blast injury In 3 cases the ethiology was questionable

No relation between the duration of the alcohol consumption and the hearing loss was established, and accordingly no support was found on the presumption that alcoholism adds to the susceptibility to noise of the organ of Corti The remarkably high incidence of acoustic trauma in the material must be viewed on the background of the large number of sailors, who for a shorter or longer period had been working in the engine room on board ship No case of hearing loss was found which was due to alcohol alone

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SPECTROGRAPHIC STUDIES OF THE SOUND QUALITY OF OESOPHAGEAL SPEECH

PRELIMINARY REPORT

By

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Laryngectomy is always followed by loss of the ability to speak which is the most important symbol of communication between mankind

The best substitute for this loss is oesophageal speech, as mentioned in the reports of a large number of investigators (Lindsay 1944, Bangs 1946, Damsté 1958) In 70 per cent of the cases (Pitkin 1953, McCall 1955, Heaver et al 1955) satisfactory sound and articulation may be obtained without artificial means

Pseudoglottis is the organ which roughly substitutes the larynx and supplies the basic frequency and tone to oesophageal speech Moolenaar-Bijl (1953), van den Berg (1957), Damsté, Kirchner et al (1963), and others, have performed extensive investigations on the localization and mechanism of pseudoglottis by roentgen cinematographic analysis of the voice-mechanism in persons with good oesophageal speech, and by measuring the pressure variations both in pharynx and oesophagus during intonation Pseudoglottis is generally considered to be situated in the lower part of the pharynx and the region of the oesophageal mouth, at the level of about the V—VI cervical vertebra. The authors mentioned above have observed that the air required for phonation collects in the upper part of oesophagus and, when liberated, causes vibration in pseudoglottis

Investigations have also concerned the co-ordination between respiration and conscious expiration of the oesophageal air, and evidence of this occurring during expiration has been seen (Burger & Kaiser 1925, Di Carlo et al 1955, Damsté, Bateman et al 1957, Levin 1962)

In the past years — since the introduction of roentgen apparatuses — endeavours have been made to clarify the voice-mechanism of laryngectomized persons by studies of the anatomic physiologic action of the oesophagus The phonetic part has mostly been left to audible observation, since the means by which the different details of phonation may be completed and clarified have been rather inadequate and difficult to handle

Instrumental phonetic means are now available, however, by which the physical characteristics of oesophageal speech may be analysed

The present investigation is limited to comprise the basic frequency of oesophageal speech and the construction of the formant of its vowels [1]

APPARATUS AND TECHNIQUE

The physical characteristics of oesophageal speech were sound spectrographically analysed by means of the Sona graph (manufactured by Kay Electric Company, Pine Brook, N J) The technical construction of the sonagraph has been closely described by Koenig et al (1946), Potter, Kopp & Green (1947), and Prestigiacomo (1957)

With this apparatus sound tests, 2 4" in length may be analysed at the frequency scale 80 to 8000 cps The sound sample is placed on the magnetic rim of a rotating disk from which it may be repeatedly reproduced, being traced on a non photographic electricity sensitive and facsimile type of paper The paper is streched round a drum rotating along the disk Thus time may be calculated from the horizontal level and frequency from the vertical level For this purpose narrow 45 cps or broad 300 cps tape filters may be used The narrow filter is more suitable for acoustic analysis as the results obtained are clearer and more distinct In the present study, the narrow filter was used for all the tests

The sonagram thus obtained may be completed and its specific points studied by analytical calculation in sections, the time of which is 5 msec and the maximum intensity 35 db, adapted specially for determination of the formant construction and of the intensity of the separate sounds

To bring out the phonetic factor of all the eight vowel sound[2] of the Finnish language each test person articulated the different vowels in alphabetical order and at random to avoid the characteristic rhythm of the tones and any associated hampering factors

MATERIAL

In the present investigation sound tests were made on 27 persons with oesophageal speech, laryngectomized for carcinoma of the larynx in 1953—1962 All the test subjects were men The material was selected from among patients in whom good oesophageal speech had been achieved and the development of speech considered completed as evidenced by repeated auditory observations over a number of years

Excluding other than oesophageal speech, all the test persons were subjected to indirect laryngoscopy, and 14 to the pertaining stroboscopy by which procedure it was ascertained the vibration of the upper oesophageal mouth and oesophageal sound

The age distribution average age 51 years and 4 months, appears from Table I The number of laryngectomized patients subjected to unilateral neck dissection — no cases of bilateral dissec tion occurred — is also given Further, the number of patients receiving roentgen after treatment is given Four patients had had roentgen treatment before the surgical interference

RESULTS

The fundamental pitch

The sound quality in persons with oesophageal speech is best illustrated by first finding a reply to the question which is the fundamental tone of oeso-

[1] According to Sovijarvi (1962) the formation region of the variable formants is as follows

F 1 = pharyngeal formant depending mostly on the pharyngeal cavity (situated behind the tongue channel)

F 2 = oral formant, depending mostly on the oral cavity (situated in the front of the tongue channel)

F 3 = subdorsal or preoral formant

F 4 = formant of the vestibule of the larynx

[2] *a* (ɑ) *e* (e) *i* (i) *o* (ɔ) *u* (u) *y* (y) *ä* (æ) *ö* (oe) The international phonetic symbols for each vowel sound are given in brackets

phageal speech? The human ear has often difficulty in distinguishing it, for which several factors may be responsible

The most significant of these factors is the lowness of the fundamental tone, to which belong numerous additional and overtones in which the sound of

Table I *Age distribution, neck dissection and roentgen treatment*

Age at time of laryngectomy	Number of cases	Neck dis section	Rtg treat ment
31–40	4	1	3
41 50	8	3	7
51–60	12	6	11
61–60	3	–	2
Total	27	10	23

To obtain a series for comparison all the vowel sounds of ten laryngectomized men of the same age group were recorded

breathing — most closely a noise — from tracheostoma and the sound of swallowing air in the oesophagus is especially noticeable The pseudoglottis vibrations were not always periodical, and then the sound disappears The amount of air in the oesophagus varies, hence the subglottis pressure varies as well Accumulation of mucus in the hypopharynx is highly inconveniencing to many patients The air used for speech has to be pressed through mucous layers of varied thickness which results in a noise, rather than in a harmonious sound

For the reasons mentioned, it is not always possible to determine the fundamental tone of persons with oesophageal speech or the vibration frequency of subglottis The measurements were made on the mid part of the vowel sound

Vibration of the fundamental tone of the several vowels varied between 32 and 72 cps The mean for the different test subjects was 36 7 to 60 5 cps, from which the mean, 50 4 cps, was obtained for the laryngectomees This mean agrees with that for the controls, 104 0 cps, the difference being one octave

A conscious change in the fundamental tone in one direction or another is almost impossible for laryngectomized persons to produce This has been unconsciously produced, the mean variations in the different test persons being 14 7 cps which corresponds to a variation of 3 to 4 tones The change achieved was quite independent of the fundamental frequency and of the vowel articulated at the moment.

The sound produced by swallowing air into the oesophagus is typical in association with oesophageal speech When speaking, this is generally not disturbing even though it is intense because it occurs temporarily before articulation or directly after The energy in the sound of swallowing is distributed between the lower border of the sonagram far beyond the upper border The intensity is remarkable as it remains at only about 5 db before or after the intensity of the following tone

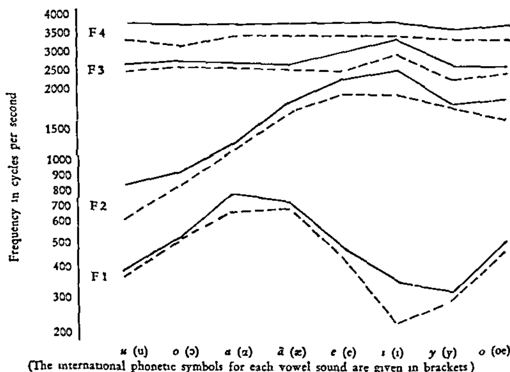
The disturbance caused by the tracheostoma sound is directly comparable with the intensity of the noise, width, and vibration area from which it emanates The power of the noise has never been observed to be of the same order of size as that of the formants which generally appear distinctly as dark horizontal lines in the sonagrams, but may, however, partly decrease the audibility of the formant which is of primary significance for identification of the vowels

Formant analysis of vowels

The second point in the present investigation was to find out what differences there are between the construction of the formants in oesophageal speech and the norms of ordinary speech.

The means for the variable formants F 1, F 2, F 3 and F 4 are graphically presented by logarithmic gradation in Fig 1, the means for the corresponding formants in the controls are illustrated as well

After removing the larynx and attaching the root of the tongue directly to the oesophagus, the vocal tract loses part of the volume of its widest resonance cavity This is evidenced also by the increase of the mean frequency of all the variable vowel formants in laryngectomees As it is well known that the decrease of the cavity volume increases the formant frequency, this result was expected, but it was surprising, on the other hand, to find that the decrease of the hypopharynx-epiglottis cavity affected all the variable formants On the basis of this result it



(The international phonetic symbols for each vowel sound are given in brackets)

Fig 1 Sequential diagram of oesophageal (———) and control ( ) speech vowel formants (F 1, F 2, F 3 F 4)

must be assumed that the mentioned cavity plays a direct role in the rise of the resonance condition in all the variable vowel formants

Of the back vowels only F 1 of *a* has risen much above its control value The results have been partly affected by the fact that, anatomically, the place of origin of *a* is farthermost in the back vowels Of all the front vowels, F 1 has clearly attained higher frequency readings than its controls, the greatest difference being in *i* when also the cavity space is at its smallest as the back of the tongue is closest to the palate

Although F 2 of *u* has risen so much above its control value and is almost on a level with the control value for *o*, differentiation of a single *u* from a single *o* is not difficult, because F 1 of the back vowels is the most important formant from the point of view of audibility

In spite of F 2 having obtained higher frequency values than its control, there is no anathomical functional order except in the back vowels, yet the high position of the tongue which promotes the illabial *e* and *i* have reached the highest differences

F 3 takes a secondary place among the back vowels since it is of no importance for furthering intelligibility of speech

However, F 3 has been demonstrated in all the subjects and has, like the throat and mouth formants, reached higher frequency values than their controls On the other hand, F 3 takes a central place among the front vowels, the comprehension of which is greatly dependant on this very formant. F 3 *e* has attained the greatest difference from its control, *i* being next in order

The fourth variable formant has been identified in a few cases — in 15 instances in none of the vowels, and in none in all the vowels — independently of the vowel concerned, by its mean frequency being about 400 cps higher than that of its control

On comparison of the mean difference between F 4 and its control, it is observed that the difference is greater than that of any other variable formant and any single formant, independently of if a front or back vowel is concerned, since removal of the larynx has caused an anatomical functional change which affects especially the arisal of the fourth variable vowel formant in the hypopharynx larynx

DISCUSSION

In the present investigation, the pitch of oesophageal speech was observed to vary considerably to the low, periodical, non-constant frequency belongs the group of additional and overtones which, decreased by the tracheostoma-oesophageal noise renders speech considerably more difficult to understand. Also Damste has pointed out these circumstances, and states that "the fundamental tone of an oseophageal voice is often difficult to determine This is because the frequency is low and because the sound is very complex, in other words the fundamental tone is accompanied by a large number of relatively strong overtones

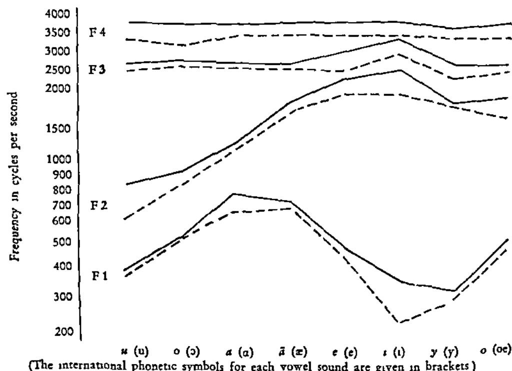
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(The international phonetic symbols for each vowel sound are given in brackets)

Fig 1 Sequential diagram of oesophageal (———) and control ( ) speech vowel formants (F 1, F 2, F 3, F 4)

SUMMARY

Using a sound spectrograph, the physical characteristics of a Finnish oesophageal speech test material were analysed Twentyseven male, laryngectomized patients with good oesophageal speech were studied The investigation was limited to study of the details which affect the fundamental pitch and formant frequencies of vowels

The pitch of oesophageal speech is highly varied to the low, periodical, non-constant frequency belong the groups of additional and overtones which, decreased by the tracheostoma-oesophageal noise, render speech considerably more difficult to understand.

The fundamental frequency which was determined in 18 laryngectomized subjects, varied in the separate vowels between 32 and 72 cps, and the mean value for the different test persons between 36 7 and 60.5 cps from which the fundamental frequency for the laryngectomees, 50 4 cps, was calculated This figure is about one octave lower than the mean for the controls Conscious changes in the fundamental sound is difficult for laryngectomees to produce, unconsciously this was done within the range of 3 to 4 tones

Owing to laryngectomy, a decrease in the resonance cavity volume caused a rise of the mean frequency for almost all the variable formants

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ANTIBIOTICS IN THE TREATMENT OF MAXILLARY SINUSITIS

By
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Divergent views prevail about the justification of using antibiotics in the treatment of acute and subacute maxillary sinusitis (*e g* van Alyea 1962 and Bryan 1957) An increasing number of investigators are of the opinion that antibiotic treatment should be limited to only selected severe cases, but it is often difficult to make the decision in practice The following is a review of a recent series of cases

MATERIAL AND METHODS

The series comprises patients with sinusitis who consulted the author during the years 1960—63 All those with acute or subacute maxillary sinusitis on whose first antral lavage a bacteriological examination could be done are included in this study. No conscious selection was performed During the first year about every other patient was given a course of antibacterial treatment immediately after the diagnostic puncture Since the results of antibiotic treatment were very satisfactory in a large number of patients, the proportion of patients who received antibiotics was definitely higher in the years 1961—63 than in the first year To eliminate the influence of the difference in the number of patients receiving and not receiving antibiotics, the results are subjected to statistical analysis The antibiotic most often administered was penicillin either parenterally or orally In some cases broad-spectrum antibiotics or sulphonamides were given Antibacterial treatment given later in the course of prolonged sinusitis is not discussed in this paper

All the patients were given decongestive nasal medication, and sinus punctures and irrigations were made at intervals averaging one week With only a few exceptions, an aqueous suspension of procaine penicillin was instilled into the antrum after the first irrigation

The samples for bacteriological examination were taken by the technique of Lumio and Oker-Blom (1957) by picking up a lump of secretion into a test-tube with forceps from the nasal lavage in a dish The specimens were cultured within twelve hours, in most cases before three hours had elapsed from the lavage

The age distribution and other information relating to the patients are shown in Tables I and II The number of punctures before recovery could not be determined for 14 patients (19 sinuses) as the patients did not report for following up examinations These patients are included in the recovered series in Tables I—VI

as apparently all of them recovered without operation, but they are not included in the study of recovery (Figures 1—6). The recovery from sinusitis was confirmed by a negative puncture in 97 per cent of the cases. In the remaining 3 per cent the recovery was confirmed by roentgenologic examination.

RESULTS

The data in Table I show that bilateral sinusitis is more common in children of school age and younger, whereas unilateral sinusitis is more frequent in adults.

Table I. *Patients who recovered following puncture and irrigation therapy.*

	Age group				Total
	Under 7	7–15	16–59	≧ 60	
Unilateral sinusitis No of patients (sinuses)	3	11	95	11	120
One species •	2	2	59	5	68
Mixed infection •	1	8	20	4	33
Sterile •	0	1	16	2	19
Respiratory pathogen(s) present •	3	7	63	8	81
Apathogens only •	0	3	16	1	20
Bilateral sinusitis No of patients	6	21	60	6	93
One species No of sinuses	7	18	74	6	105
Mixed infection •	2	14	26	4	46
Sterile •	3	10	20	2	35
Respiratory pathogen(s) present •	3	29	87	8	127
Apathogens only •	6	3	13	2	24
Total number of patients	9	32	155	17	213
Total number of sinuses	15	53	215	23	306

Table II. *Patients requiring operative treatment.*

	Age group			Total
	7–15	16–59	≧ 60	
Unilateral operation No of patients (sinuses)	1	13	1	15
One species •	0	6	0	6
Mixed infection •	1	3	0	4
Sterile •	0	4	1	5
Respiratory pathogen(s) present •	0	9	0	9
Apathogens only •	1	0	0	1
Bilateral sinusitis with unilateral recovery No of patients	1	5	0	6
Bilateral operation •	3	10	0	13
One species No of sinuses	2	9		11
Mixed infection •	3	6		9
Sterile •	1	5		6
Respiratory pathogen(s) present •	4	9		13
Apathogens only •	1	6		7
Total number of patients	4	23	1	28
Total number of sinuses	7	33	1	41

DISCUSSION

Lystad to Kortekangas

I understood Dr Kortekangas to imply that in two series of patients under treatment, in the first group he had made punctures of the anthrum and in the second group punctures combined with antibiotic therapy The results of the treatment in the two groups of patients did not differ, and the conclusions was that antibiotic treatment in addition to punctures in bacterial sinusitis was unnecessary The results without antibiotic treatment would be equally good

Is it not probable that such relatively frequent punctures of the maxillary sinus will result in the introduction of potentially pathogenic bacteria from the nasal cavity into the sinus and reestablishment of an infection with other bacteria than those primarily isolated?

Have you observed any changes in the bacterial flora in the course of these treatments with frequent punctures? If so, have sensitivity tests been done, and has the antibiotic treatment been changed accordingly?

In addition to the two above mentioned groups of patients getting different therapy, would it not be useful giving a third group of patients antibiotic treatment only without punctures? Only by comparing the results of the three groups, conclusions can be drawn as to whether antibiotic drugs have any effect Possible reinfections by frequent punctures will then be avoided.

Kortekangas to Lystad

In reply to Dr Lystad's question, I dot not think that a bacterial superinfection as a result of repeated antral puncture and irrigation plays any role in practice I have observed several patients from whom cultures were made repeatedly in connection with punctures The rule was that the secretions from all except the first irrigation were sterile This was often observed also in the patients operated later, but these patients comprised a special group with sinuses very prone to superinfection Acute exacerbations were occasionally observed in the group of patients that responded to puncture and irrigation therapy The bacteriological results for repeated cultures from these patients showed that the source of superinfection apparently was the environment as in "natural" infections.

As to the question of the effect of antibiotics without punctures and irrigations, I should like to say that the effect cannot be estimated from my material which only reveals the additional effect of antibiotics in connection to puncture and irrigation treatment. Remembering the difficulties of reliable diagnosis and the very remarkable tendency for spontaneous recovery from maxillary sinusitis, it would be difficult to arrange an objective comparative study of the effect of antibiotics alone against the effect of punctures and irrigations The authors who have tried this have been most careful in their evaluation of the results and I have not seen any study with clear data on this point although opinions are usually expressed about the value of antibiotics

THE BACTERIAL FLORA OF SINUSITIS WITH AN IN VITRO STUDY OF THE BACTERIAL RESISTANCE TO ANTIBIOTICS

By

Arve Lystad Peter Berdal and *Lauritz Lund Iversen*

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The bacterial flora of sinusitis has been the subject of much investigation Mixed infections and the presence of saprophytic bacteria have often been reported, and during the last years the presence of Staphylococcus aureus in sinuses has been frequently reported It seems to be a common opinion that Staphylococcus aureus has an increased importance as the cause of infections in the upper respiratory tract

However, the presence of saprophytic bacteria and yellow staphylococci may frequently be a result of contamination from the nose on collecting the specimens (Palva et al, 1962, Fredette & Forget, 1961)

Very often the material for bacteriological examination has been obtained by puncture of the maxillary sinus and collection of the saline irrigation fluid evacuated through the nose Such sampling must necessarily involve contamination from the nasal cavity where staphylococci predominate in the bacterial flora (Bjorkwall, 1950, Rippon & Vogelsang 1956 a o)

The yellow staphylococci and other contaminants from the nose, e g neisseria, diphteroids and micrococci may overgrow and mask the presence of causal microbes contained in sinus secretions This may give rise to false conclusions

The main purpose of this work was to assess the role of the yellow staphylococci in sinusitis Further, we wished to study which kinds of bacteria are the most frequent causes of sinusitis today, and to examine their sensitivity to antibiotics in vitro

MATERIAL AND METHODS

The material consists of 269 patients suffering from sinusitis The diagnosis was verified by clinical methods and X ray examinations The patients were partly examined and treated at the Outpatient Clinic of the Ear, Nose and Throat Department of Rikshospitalet, Oslo, partly hospitalized in the latter department during the period from October 1961 to January 1963 The distribution of patients according to age and sex is shown in Table I

As shown in Table II, the patients are divided in five groups according to the duration of sinusitis Cases with a duration less than 3 months are classified as acute, with a duration between 3 and 12 months as subchronic and with a duration of more than 12 months as chronic sinusitis In group IV we find cases of

Table I *Age and sex distribution*

Age	< 10	11–20	21–30	31–40	41–50	51–60	61–70	> 70	Total
Male	33	32	13	17	22	21	11	2	151
Female	11	20	22	20	17	21	6	1	118
Total	44	52	35	37	39	42	17	3	269

Table II *The distribution of cases according to the duration of sinusitis*

	I Acute upto 3 months	II Subchronic 3–12 months	III Chronic > 12 months	IV Unknown casually detected	V Records unavailable	Total
Number of cases	105	29	110	12	13	269

unknown duration, accidentally detected, and in the last group V we find cases where the patients' records were unavailable

From 233 patients sinus secretions were obtained and from 36 patients only nasal swabs from the middle meatus were taken

Sensitivity tests were performed on 80 strains of Haemophilus influenzae, 59 strains of Diplococcus pneumoniae, 43 strains of Staphylococcus aureus, 5 strains of Neisseria meningitidis, 4 strains of Proteus species, 3 strains of non-hemolytic streptococci isolated primarily by anaerobic methods, 2 strains of Streptococcus hemolyticus, 2 strains of Aerobacter species and, finally, on one strain each of Neisseria pharyngis, E coli and Enterococcus, altogether 201 strains

Samples for bacteriological examination were in 123 cases collected by puncture of the maxillary sinus and aspiration of the secretion without instillation of saline In 110 cases saline was instilled into the maxillary sinus and sinus washings evacuated through the nose were examined

Nose specimens were taken with very slender swabs through a sterile nasal speculum from the middle meatus

All samples from sinuses were streaked out within 1—2 hours after puncture, and nasal swabs streaked at once Direct smears were stained by Gram's method with dilute carbol fuchsin as counter stain Gramnegative rods then stand out clearly The samples were spread on blood agar plates and incubated at 37° C for 1—2 days In order to isolate haemophilus strains, all cultures on blood agar media were cross-streaked with yellow staphylococci Further, the samples from sinuses were also spread on blood agar plates and incubated for 2—3 days in an anaerobic jar

The microbes isolated were identified by the usual biochemical methods and Gram staining Haemophilus influenzae was identified by the satellite phenomenon, and Diplococcus pneumoniae was identified by the optochin test On all the staphylococci the coagulase test was performed

Sensitivity tests were performed by an agar diffusion technique described by

Ericsson et al (1954) Because of very scanty growth of H influenzae on the standard medium for sensitivity tests, chocolate agar plates had to replace the standard medium in the tests of haemophilus strains

The strains were classfied as sensitive (likely to yield to therapy in general infections ordinary dosage), fairly sensitive (likely to yield to therapy in general infections, high dosage), relatively resistant (likely to yield to therapy in organs in which the agent may be concentrated) and resistant (therapeutic effect un likely) (Ericsson & Swartz Malmberg, 1957)

The paper discs were delivered by Karolinska Sjukhuset, Stockholm, and the criteria for reading was followed (Ericsson et al, 1954) The zones of doktacillin were read according to Wahlquist (1961)

The influence of the composition of the chocolate agar medium on the action of sulphonamides, makes sensitivity tests on H influenzae uncertain Therefore the results of testing H influenzae to sulphonamides are not reported

RESULTS

Table III shows the distribution of the various bacterial isolations according to the duration of sinusitis In 233 sinus secretions examined, the bacteria most frequently isolated are Haemophilus influenzae and Diplococcus pneumoniae,

Table III *Distribution of the various bacterial species among the five groups*

Cultivation	Sinus secretions					Total	Nasal samples (no sinus secr)	Total number of cases
	I	II	III	IV	V			
H. influenzae	18	5	15	3	1	42	12	54
Diplococcus pneumoniae	17	4	15	1	4	41	7	48
Staphylococcus aureus	4	2	5	2	0	13	3	16
Anaerobic streptococci	3	2	4	0	0	9	0	9
Streptococcus haemolyticus	3	1	2	0	0	6	1	7
Neisseria meningitidis	2	0	1	0	0	3	0	3
Proteus sp	1	0	2	0	0	3	0	3
Aerobacter sp	1	0	1	0	0	2	0	2
Enterococci	0	0	1	0	0	1	0	1
Klebsiella ozænae	0	0	1	0	0	1	0	1
H influenzae + Diplococcus pneumoniae	8	1	7	1	0	17	5	22
H influenzae + Streptococcus haemolyticus	0	0	1	0	0	1	0	1
H. influenzae + Staphylococcus aureus	0	0	1	0	0	1	3	4
Dipl. pneum. + Staphylococcus aureus	0	0	4	0	2	6	0	6
Dipl. pneum. + N meningitidis	0	0	1	0	0	1	1	2
Anaerobic mixed flora	1	0	2	0	0	3	0	3
Other monobacterial findings	7	3	5	1	2	18	3	21
Other mixed findings	7	2	7	1	0	17	0	17
No growth	15	8	22	3	0	48	1	49
Total	87	28	97	12	9	233	36	269

in pure culture or together The group "no growth" is also large and consists of 48 cases H influenzae and Diplococcus pneumoniae are equally distributed among the acute and chronic group Anaerobic streptococci were isolated in 9 cases and hemolytic streptococci in 6 cases Both bacteria were equally distributed among the acute and chronic group Anaerobic mixed flora was found in 3 cases, 1 in the acute and 2 in the chronic group

The bacterial species from nasal samples where no sinus secretions were taken, show the same distribution

Table III and IV show that the yellow staphylococci were isolated from 20 sinus secretions, 13 in pure culture and 7 mixed with other bacteria. Ten patients with findings of yellow staphylococci suffered from chronic sinusitis

In the 7 mixed cultures pneumococci were the second organism 6 times and haemophilus once By direct microscopy bacteria looking like staphylococci were few or undetectable In 5 of the cases, belonging to the chronic group, yellow staphylococci were also found in cultures of nasal swabs In the remaining 2 cases, belonging to group V, nasal swabs had not been taken at the same time. All 7 mixed cultures were of sinus washings

Nine of the 13 pure cultures of yellow staphylococci came from sinus washings and only 4 from aspirates (Table IV) In these 9 samples few or no bacteria were seen in Gram smears, and when a few staphylococci were seen, the nasal samples gave abundant growth of staphylococci on blood agar plates

Four cultures from aspirates remain By direct microscopy bacteria were not

Table IV *Frequency of isolation of different species according to the manner of isolation*

Bacterial species	Sinus secretions			Nasal samples only	Total
	Aspirates	Washings	Total		
H. influenzae	34 (22)*	27 (20)	61 (42)	20 (12)	81 (54)
Diplococcus pneumoniae	32 (21)	33 (20)	65 (41)	13 (7)	78 (48)
Staphylococcus aureus	4 (4)	16 (9)	20 (13)	6 (3)	26 (16)
Anaerobes	10 (8)	2 (1)	12 (9)	0	12 (9)
Streptococcus haemolyticus	5 (4)	1 (1)	6 (5)	1 (1)	7 (6)
Other pathogens	6 (5)	5 (5)	11 (10)	0	11 (10)
Apathogenic bacteria	12 (6)	23 (12)	35 (18)	3	38 (18)

* Figures in brackets represent pure cultures

Table V *Antibiotic sensitivity of 80 Haemophilus influenzae strains in per cent*

Characterization	Sensitive	Fairly sensitive	Relatively resistant	Resistant
Penicillin	0	56	25	19
Streptomycin	87	10	1 5	1.5
Chloramphenicol	100	0	0	0
Oxytetracycline	98	2	0	0
Erythromycin	47 5	50	2.5	0
Doktacillin*	57	28 5	9.5	5

* Only 63 strains tested

seen in 3 samples, and in addition there were only found few colonies in the culture From the nasal samples several yellow staphylococci were isolated from 2 of the 3 cases In the third case, a nasal sample was lacking

In the remaining single case, the nasal sample showed no growth, the aspirate from sinus showed heavy growth of yellow staphylococci and the direct smear showed several heaps of Gram positive cocci

The results of sensitivity tests within the group of H influenzae strains expressed in percentage are shown in Table V Chloramphenicol, oxytetracycline and streptomycin are most effective against H influenzae in vitro Next to these antibiotics range doktacillin and erythromycin About 44 per cent of the strains show resistance or relative resistance to penicillin in vitro Compared with penicillin doktacillin seems to be more effective against H influenzae in vitro, when only 15 per cent of the strains show resistance or relative resistance to doktacillin

Table VI shows the distribution of sensitivity, expressed as percentages, within the group of Diplococcus pneumoniae strains With the exception of streptomycin, all the antibiotics are effective against Diplococcus pneumoniae in vitro

Table VI *Antibiotic sensitivity of 59 Diplococcus pneumoniae strains in per cent*

Characterization	Sensitive	Fairly sensitive	Relatively resistant	Resistant
Sulphonamide	79	15	2	4
Penicillin	93	7	0	0
Streptomycin	15	29	54	2
Chloramphenicol	100	0	0	0
Oxytetracycline	100	0	0	0
Erythromycin	100	0	0	0
Doktacillin*	92	8	0	0

* Only 26 strains tested.

Table VII *Antibiotic sensitivity of 43 Staphylococcus aureus strains expressed in per cent*

Characterization	Sensitive	Fairly sensitive	Relatively resistant	Resistant
Sulphonamide	72	9	8	11
Penicillin	52	16	16	16
Streptomycin	77	9	7	7
Chloramphenicol	96	2	2	0
Oxytetracycline	79	5	0	16
Erythromycin	96	2	2	0
Methicillin*	87	10	3	0

* Only 39 strains tested.

Table VII shows the distribution of sensitivity of Staphylococcus aureus strains isolated from the upper respiratory tract A high percentage of these strains seem to be sensitive to all the antibiotics tested The highest incidence of resistance is found towards penicillin, oxytetracycline and sulphonamides

Of the other different strains tested 5 strains of Neisseria meningitidis were sensitive to all of the antibiotics Of the 3 strains of non hemolytic streptococci one was resistant to sulphonamides Likewise in the group of hemolytic streptococci one strain was resistant to sulphonamides The 4 Proteus strains and the E coli strain were sensitive to sulphonamides, streptomycin and chloramphenicol, but resistant to penicillin, oxytetracycline, erythromycin and doktacillin The 2 Aerobacter strains were sensitive to all the antibiotics but penicillin and erythromycin The one Neisseria pharyngis strain and the Enterococcus strain were sensitive to all of the antibiotics tested

DISCUSSION

Methods

As far as possible, the samples for bacteriological examination were collected by puncture of the maxillary sinus and aspiration of the secretion without instillation of saline By using this technique we hoped to reduce contamination from the nasal cavity Contamination is then limited to those bacteria which may be carried into the sinus by the puncture needle The few contaminants in the samples taken by aspiration may be detectable only by cultivation on solid media but not by direct microscopy It is therefore important that Gram smears are examined and the results compared with the cultures

✓ One difficulty inherent in the method of aspiration is that in some cases no secretion can be obtained Therefore sinus washings had to be examined in 110 cases

It is very important that very slender, sterile swabs can be used to take nose specimens and that the specimens are taken through a sterile nasal speculum to avoid the bacterial flora of nasal vestibulum

✓ It is also of great importance that the nasal swabs and the maxillary secretions are spread on culture media at once or within few hours The organisms present, especially H influenzae pneumococci and meningococci, will soon dry up and die before being spread

Results

When comparing our results with those obtained in some recent Scandinavian studies, we find that there are some differences Sparrevohn & Buch (1946) in a material of 198 sinuses found that in acute cases pneumococci and in chronic cases hemolytic streptococci are the most frequent pathogens They report Staphylococcus aureus in only 4 % of the cases Sterile cultures were reported in 31 % of the cases The role of H influenzae was small Urdal & Berdal (1949) could not demonstrate any difference between acute and chronic cases Their findings showed pneumococci to be the most frequent cause, followed by H influenzae Streptococcus hemolyticus played a minor role in their material of 81 cases of maxillary sinusitis They specifically claimed that the staphylococci play no role

The work of Bjorkwall (1950) shows that in 96 cases of purulent maxillary

sinusitis, the most frequently isolated bacteria were pneumococci and hemolytic streptococci Staphylococcus aureus was isolated in 8 % and H influenzae in as few as 4 % of the cases In 13 cases the sample was sterile

The results of Tunevall (1952) correspond more with those of Urdal & Berdal (1949) and with our work The role of pneumococci and H influenzae is important The role of Staphylococcus aureus is small

A paper by van Dishoeck & Franssen (1957) reported H influenzae to be most frequent (47 %) in 215 cases, while Mounier Kuhn (1953) and Piquet et al (1956) found H influenzae in very few samples In the work of Piquet et al (67 cases), pneumococci did not appear at all

Of the 88 cases of chronic maxillary sinusitis subjected to bacteriological analyses by Palva et al (1962), both H influenzae and Diplococcus pneumoniae were found in 10 %, while the figure of Streptococcus viridans was as high as 30 % Thirty eight per cent of the samples were sterile

Our work indicates that the most important bacteria in sinusitis, both acute and chronic, are H influenzae and Diplococcus pneumoniae The role of Streptococcus hemolyticus is slight The distribution of anaerobic streptococci equally between the acute and chronic group is very interesting It is also noteworthy that monobacterial infection prevailed in long standing cases as much as in acute cases

Fortyeight samples were sterile On examining all the patients' records more closely, we found that of these 48 patients 27 were under treatment or recently treated with different antibacterial drugs Twelve patients suffered from allergic diseases in the upper respiratory tract From one patient the aspirated sample was completely dry In the remaining 8 cases we have no explanation why the findings are negative In one of these latter cases, small Gram negative rods could be demonstrated in direct smears from several samples However, this bacterium we were not able to cultivate

The two groups "other monobacterial findings" and "other mixed findings" (Table III) consist of 35 cases From these patients there were isolated apathogenic bacteria such as Neisseria pharyngis, diptheroids, micrococci and Streptococcus viridans Of these 35 patients, 16 were recently treated with antibacterial drugs Twelve of the patients suffered from allergic diseases in the upper respiratory tract In the remaining 7 cases we have no explanation why no pathogens were isolated The findings probably were contaminants from the nasal cavity

In only one single out of 233 cases of sinusitis, it may be said with great probability that Staphylococcus aureus has caused sinusitis The importance of yellow staphylococci as the cause of sinusitis, seems to have been grossly exaggerated The frequent isolations of yellow staphylococci by other workers (Mounier-Kuhn, 1953 and Fredette & Forget, 1961), are probably caused by different and unsatisfactory sampling methods It is very important that the samples are taken in a correct way All cultures from sinus washings have to be judged with reservation Staphylococcus aureus appeared in one half per cent of the cases a figure supporting the view that the larger percentages sometimes

reported (Bjorkwall, 1950, Mounier Kuhn, 1953 and Fredette & Forget, 1961) were mainly due to contamination from the nasal cavity

The relatively frequent occurrence of H influenzae in some of the recent studies and in our study, corresponds to recent investigations on the microbial flora in infections of the air passages Nielsen (1945) found a high frequency of H influenzae in 802 cases of acute otitis and likewise Henriksen (1936) in 59 cases of acute bronchitis and bronchopneumonia Sellerholm & Åhlander (1960) in a material of 2882 cases of acute otitis media, found that H influenzae plays an increasing role as causative agent in acute otitis

Our opinion is that the variation in bacteriological findings in sinus secretions, is more a consequence of different sampling methods than of real difference in the bacterial flora of sinusitis

Sensitivity tests

Recent works concerning the sensitivity of H influenzae towards antibiotics in vitro, correspond with our findings Zinnemann (1960) emphasizes the agreement that excists concerning the effect of chloramphenicol and streptomycin towards H influenzae Some years after the discovery of penicillin, studies showed that penicillin had no effect against these infections This was a general view until Gordon & Zinnemann (1945) and Hewitt & Pittman (1946) observed penicillin sensitive strains of H influenzae in some in vitro studies Engbæk (1949) and Tunevall (1951) did not share this opinion In an in vitro study of 63 strains of H influenzae, Tunevall showed that the concentration of penicillin in serum had to be extremely high to get the desirable effect of this antibioticum His studies showed that chloramphenicol, aureomycin, terramycin and streptomycin were the drugs of choice

Omland (1962) has studied the sensitivity of 153 strains of H influenzae in vitro to different antibiotics and his results seem, with only small differences, to correspond with our findings

The sensitivity of Diplococcus pneumoniae in vitro seems to remain unchanged

The staphylococci here tested, were mostly sensitive

So far as any conclusions can be drawn from in vitro tests, it seems likely that chloramphenicol and oxyterracycline should in the first place be used in H influenzae infections General clinical experience has also confirmed this view as to sinusitis caused by H influenzae

Penicillin and/or sulphonamides should be used in infections caused by pneumococci The broad spectrum antibiotics should be reserved for infections caused by other bacteria or by mixed bacterial flora A mixture of pneumococci and haemophilus is relatively frequent in sinusitis Against such a flora, chloramphenicol or tetracyclines are the drugs of choice Our results show that doktacillin and erythromycin are drugs that can be used, but in the second place, or if the treatment has to be changed for other reasons

The material of other strains where sensitivity tests in vitro were performed, was so small that hardly any conclusions could be drawn

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SUMMARY

Maxillary secretions and nasal swabs from 269 patients with sinusitis have been bacteriological examined

The microbes most frequently isolated were Haemophilus influenzae and Diplococcus pneumoniae in pure culture or together The role of Streptococcus hemolyticus and anaerobic bacteria in sinusitis is relatively slight The importance of Staphylococcus aureus as the cause of sinusitis seems to have been exaggerated and is in fact very slight

Most of the infections were monomicrobial both in shortstanding and long-standing sinusitis In bimicrobial infections, the flora most often consisted of the two abovementioned microbes

Sinus washings give unreliable results Secretions obtained by aspiration without saline washing of the antrum give more reliable results Nasal samples taken with slender swabs through a nasal speculum from the inner part of the nasal cavity and meatus medius give valuable information about the bacteria causing sinusitis

In vitro sensitivity tests of H influenzae isolated, indicate that chloramphenicol and oxytetracycline are the most active antibiotics, closely followed by streptomycin and erythromycin The susceptibility of some, but not all strains of H influenzae to doktacillin is of nearly the same order

The in vitro sensitivity of Diplococcus pneumoniae to antibiotics seems to remain unchanged

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OPERATIVE RESULTS IN BELL'S PALSY

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The term Bell s palsy is nowadays reserved for cases of peripheral facial palsy which cannot be attributed to any obvious local process The etiology has still not been definitely clarified, and so there are greatly varying theories in its origin

Most authorities have accepted Kettel s theory he assumes the cause to be vasospasm of the branches of the external carotid artery supplying blood to the facial nerve (petrosal artery and stylomastoid artery) (Kettel 1947, Hilger 1949) This vasospasm causes ischemia of the nerve and its sheath leading to increased capillary permeability and oedema All this results in compression of the nerve, which in turn leads to pressure on the capillaries and veins, and to further increase of oedema so that finally there is a kind of vicious circle

The exit of the facial nerve from its bony canal is in the stylomastoid foramen At this point the nerve is most liable to compression and the resulting nutritional disturbances (Cawthorne 1946, Kettel 1947, Sullivan 1952) In the vertical portion, in particular, oedema has been noted, and in the nerve sheath even slight ecchymosis (Cawthorne 1946) These hemorrhages may even occur in the tympanic portion of the nerve (Williams 1959)

The changes in Kettel s opinion are not limited to the nerve and its sheath only considerable tissue changes are observed in an extensive area of the surrounding bone even in the mastoid cells Kettel s 1947 study contains the following statement Then it must be concluded that in 20 per cent of the cases of Bell s palsy bony necrosis of the mastoid cells especially around the stylomastoid foramen has been demonstrated, but no signs of round cells infiltration or granulation tissue In 36 per cent of the cases similar changes were, moreover, found in the wall of the facial canal ' Though he himself never observed anything like this, Williams (1959) believes such changes are possible

Bell s palsy has earlier been termed rheumatic facial paralysis and also paralysis due to exposure to cold (paralysis nervi facialis e frigore) Even Kettel (1954) thinks exposure to cold plays a part in the origin of this condition Patients with facial palsy often suffer considerable pain in the region of the ear at the initial stages, and this may be the reason why this disease is sometimes still called rheumatic paralysis Many investigators consider such pain a sign of grave prognosis (Tumarkin 1936 Sullivan and Smith 1950, Cawthorne 1951, Dalton 1960)

Attempts have been made to predict the prognosis in Bell s palsy by various

methods The most common of the these is excitation of the nerve by means of faradic current Duel (1933), Ballance (1934) Tickle (1945) and Cawthorne (1946) stress the importance of this test in evaluating the chances of recovery of the nerve, whereas Kettel (1947) Martin (1941) and Dalton (1960) do not rely on the results of the faradic test It is indeed claimed by McGovern and Hansel (1961) that there is no reliable method for evaluating and to what extent the nerve is likely to recover function Martin (1953) has noted that the function of the facial nerve often returns even in the absence of any faradic response Electromyography seems after all to be the method permitting most reliable evaluation of irreversible atrophy of the nerve (Taverner 1955) The majority of cases of Bell s palsy recover with conservative treatment or even spontaneously Only 10 to 15 per cent (Tickle 1945 Sullivan and Smith 1950) do not recover with medication Since vasospasm is now considered the most important factor, early treatment with vasodilators is advisable A great variety of preparations have been used and they do not seem to differ much in regard to vasodilating properties Blocking of the stellate ganglion has been employed in recent years to produce vasodilatation and seems to be highly effective especially during the first few days (Cohen 1960) Good results can evidently be obtained without any treatment whatever (Hopp and Hambley 1961), yet is seems that some therapy is indicated to strengthen the patient s morale Electrotherapy is also widely used and galvanic current is considered to keep the muscles in good condition though it hardly cures the cause of the disease (Botman and Jongkees 1955)

As already stated some of the cases of palsy fail to recover by conservative methods These cases have been treated surgically with success for 30 years now The first decompression of the facial nerve was performed by the Austrian Alt as long ago as 1908 Ballance and Duel in 1932 published an article on the surg cal treatment of the facial nerve which stimulated much interest among otologists in different parts of the world

Since it is well known that in most cases this condition is cured by conserv ative means surgical treatment is not considered indicated at the early stage but it still remains an open question how long one should wait for spontaneous recovery of facial function It is generally agreed that, if function has not returned within 2 months surgical facial nerve decompression is indicated then comes the added risk of nerve degeneration which renders even surgical treat ment useless from the point of view of restoration of nerve function (Martin 1940 Williams 1946 Kettel 1947) In the opinion of some authors 2 months is too long and they advise waiting only one month (Cawthorne 1951, Korkis 1958) Ballance and Duel recommend a shorter period still

Facial nerve decompression aims at exposure of the nerve in its bony canal between the stylomastoid foramen and the oval window Most commonly the operation is started w th a retroa r c lar [illegible]

started at the tympanic end of the nerve (Kettel 1959) O Meurman (1958)

does not consider a mastoidectomy necessary He performs the operation through an endaural approach exposing first the tympanal portion of the nerve, and then the nerve itself from this area down to the stylomastoid foramen It may indeed be asked whether mastoidectomy is imperative since it has not been established that mastoid cell infection plays any part in the origin of Bell's palsy (Kettel 1954, Jongkees 1954)

OUR OWN STUDIES

Case material

The study is based on 34 cases of Bell's palsy operated on at the Otolaryngological Hospital of the University of Helsinki during the period 1947—1961, which covers 15 years A follow-up study on all operated patients was conducted in 1961 and 1962 The majority of the pasients (26 in number) came to the clinic for examination, only 8 failed to come because of the long journeys required, but each of these latter returned the questionnaire with their replies The patients were from different parts of the country This was perhaps one of the reasons why the conservative treatment preceding operation had differed widely Seventeen patients had received vasodilating drugs in addition to other therapy. Some had been given vitamin B preparations In many cases electrotherapy had been used also preoperatively Despite the conservative treatment, all patients in the series had complete facial paralysis at the time of operation Therefore a closer investigation of the conservative methods adopted does not seem called for here

The patients are classified by age as follows (Table I)

Table I *Age and sex*

Age	Male	Female
1–10 years		1
11 20 »	2	2
21–30 »	4	4
31–40 »	3	5
41–50 »	1	4
51–60 »	2	3
61–70 »	1	1
71–80 »	1	–
Total	14	20

The youngest patient was a girl aged 8 years and the oldest a man of 72 The number of patients operated on each year was about the same, apart from a slight increase in surgically treated cases in the last few years

In the past history, special attention was paid to three points

1) The duration of disease prior to operation,
2) pain as the initial symptom, and
3) exposure to cold

Most of the patients were admitted for operation when 2—3 months had passed since the onset of the disease In 3 cases operation was performed less than 2 months after the onset In 4 cases the patients sought surgical assistance at the late stage they had a history of Bell's palsy for, respectively 9 months, 2½ years, 2½ years, and 3 years A total of 12 patients complained of pain having been the early symptom In 8 cases the onset was referred to exposure to cold We shall return to these symptoms later in this study

Roentgenological findings

X ray examination was made in all the cases, except 6 treated during the early years of the study Table II shows the extent of the mastoid cell system

Table II *Extent of mastoid cell system*

Large	15
Moderate	9
Small	4
Not examined by x rays	6
Total	34

The greater part of the patients, thus, had a large mastoid cell system In none of the cases was there cloudiness in this area It should be noted that, on operation, all the cell systems that were opened proved healthy, including even those 6 cases in which no roentgen films had been taken Neither in the Fallopian canal nor in the stylomastoid foramen could roentgenological bone changes be demonstrated in a single case

Technique of operation

As stated in the foregoing, the facial nerve can be exposed in several ways The choice of technique depends mainly on the operator It seems, however, that the technique chosen does not in the end affect the ultimate result appreciably in practice the most important point seems to be that the operation can be made without injuring the nerve itself and the structures intimately adjoining it

In the present series the technique already developed by Ballance and Duel was frequently used the approach is through a retroauricular incision, the bone is widely exposed, mastoidectomy performed, and the nerve sought in the stylomastoid foramen, where it is exposed up to the area of the oval window The nerve sheath is then slit longitudinally It may sometimes be difficult to find the nerve in the stylomastoid foramen Exposure may also be started at the tympanic end of the nerve in the vicinity of the oval window, where the nerve is easily found Both of the above-described methods include a mastoidectomy, which is performed before proceeding to exposure of the nerve This technique is not doubt advantageous from the point of view that a wide field of operation is obtained with good visual exposure of the facial canal — As shown by X ray

examinations, none of the mastoid cell systems in the series revealed inflammatory changes On the basis of this observation a technique was developed which does not include a mastoidectomy The operative approach is through an endaural incision (O Meurman 1958) The nerve is sought in the area of the oval window, where it is easy to find Manipulation in the region of the stylomastoid foramen may occasionally cause difficulty because of the small space available To evade these difficulties a endaural incision may be substituted for the retroauricular one, using otherwise O Meurman's technique

Table III illustrates the techniques of operation here used

Table III *Technique of operation*

Groups	Endaural incision	Retroauricular incision		Cases
		Exposure directed centrally	Exposure directed peripher	
Mastoidectomy	–	10	12	22
No mastoidectomy	10	–	2	12
Total	10	10	14	34

The method of inducing anesthesia varied in the earlier years a local anesthesia was used in all cases with the exception of children, whereas in recent years general anesthesia has been used almost invariably Our series includes 18 cases of local and 15 of general anesthesia

Findings at operation

As will be remembered no pathological changes were disclosed on roentgenological examination In the 22 cases in which a mastoidectomy was done, no secretion was found in the mastoid cells and the mucosa was entirely healthy throughout Special attention was paid to the area of the stylomastoid foramen In 10 cases there were distinct pathological changes in this area although X-ray examination showed no evidence of this In 3 cases the bony canal was definitely narrowed, causing compression on the nerve, while in 7 cases it was normal but showed distinct scar formation between the bony wall and the nerve sheath The scar tissue in all cases extended beyond the stylomastoid foramen The occurrence of this scar tissue suggests that there must have been some kind of aseptic inflammation in immediate proximity to the nerve Those cases in which the bony canal was narrowed are also indicative of inflammation These stenoses, it is true, may also be congenital anomalies In 4 cases a defect was noted in the bony capsule of the tympanic portion of the nerve, these must be regarded as congenital anomalies since it is difficult to understand that osteitis could cause so locally limited changes

Note was made of the appearance of the nerve at operation The results are given in Table IV, where the cases are classified into three groups according to the condition of the bony canal When speaking below of the nerve, we refer to the exposed part

Table IV *Appearance of nerve*

Appearance of nerve	Defect in capsule	Narrowing in stylomastoid foramen		Nerve canal normal	Cases
		Osseous change	Scar formation		
Normal	2	1	1	8	12
Oedematous	1	1	2	6	10
Horizontal portion oedematous	1			2	3
Vertical portion oedematous			2	2	4
Atrophic				1	1
Horizontal portion atrophic				1	1
Vertical portion atrophic		1	2		3
Total	4	3	7	20	34

Owing to the small number of cases in the series, no definite conclusions can be drawn from the table It shows, however, that in about 60 per cent of the cases the appearance of the nerve differed from normal If the bony canal was normal, the nerve was either of normal appearance (8 cases) or most of the pathological changes involved the entire region of the nerve (7 cases) Further it is seen that, in cases of capsular defect, there were no changes in the vertical portion of the nerve, and in lesions of the area of the stylomastoid foramen the horizontal portion did not show changes In the presence of narrowing of the bony canal in the region of the stylomastoid foramen, there was a definite tendency for the changes to involve the area of the vertical portion of the nerve (10 cases, in 5 vertical portion pathologically changes, in 3 entire nerve oedematous) However, if there was a capsular defect, the changes tended to occur in the horizontal portion or in the whole nerve In 3 of those 4 cases in which the preoperative duration of disease must be considered too long (9 months, 2 1/2 years, 2 1/4 years and 3 years) the nerve was found to be macroscopically normal, but in one case the nerve was intensely atrophic throughout Operation was resorted to in these 4 cases because the patients themselves definitely wished it, though no recovery could be expected

Result of treatment

In evaluating the results of operation, attention was first directed to the function of the facial nerve as a while, and in addition to the mobility of each of the facial branches The degree of their function was rated on a 4 point scale from 0 to 3 as follows

0 — total immobility of branch,
1 — distinct mobility,
2 — slight limitation of movement,
3 — perfect mobility

The function of the entire nerve can then be expressed by the average of the functions recorded for the individual branches

When should operation be resorted to?

Finally the recovery should be dealt with in the light of the past history. Our case material included 4 cases in which operation may be said to have been delayed too long (duration of disease 9 months, 2 1/2 years, 2 1/2 years, and 3 years). Here operation resulted in no improvement whatever. The greater part of the cases were operated upon within 3 months or less of the onset of palsy. In this group there were 3 cases with a history of palsy for one month, one month, and 1 1/2 months respectively. In the remaining cases in this group the preoperative duration of palsy varied from 2 to 3 months. It appeared from the study that the results as regards facial function were not affected by the duration of disease, so long as it was shorter than 3 months.

Effect of pain and exposure to cold

A total of 12 patients complained of pain. One of them belonged to the group with too long a history of disease before operation. For the remaining 11 patients in this group, the figure representing average recovery of the branches is 1.9, which corresponds to the average for the total material. Thus pain as an early sign cannot be considered of any prognostic significance, favourable or otherwise. Eight patients stated that the palsy had begun after exposure to cold. This group, too, included one case in which operation had been delayed too long. For the remaining 7 patients the average denoting recovery is 2.4. It may be added that facial function became entirely normal after operation in 2 of these cases. Although the number of cases in this group is not large, it would seem that exposure to cold preceding the palsy is prognostically a favourable sign.

SUMMARY

The series consisted of 34 patients operated on for Bell's palsy. In none of the cases were roentgenological changes seen in the mastoid cells. Even though operation revealed bony stenosis at the exit of the nerve canal in 3 cases, this could not be demonstrated in roentgenograms. Indeed, taking account of the nature of these changes and the thickness of the temporal bone, we can say that the pathological changes associated with Bell's palsy are almost impossible to detect roentgenologically. And if these is roentgenological evidence of pathology, the changes appear to be unrelated to Bell's palsy.

The disease occurs in both sexes and at all ages. The youngest patient was 8 years old and the oldest 72.

The majority of the patients were operated on within 2 to 3 months of the onset. To perform the operation earlier was not found to give any advantage. In 4 cases operation was clearly delayed too long (9 months, 2 1/2 years, 2 1/2 years and 3 years). These operations failed to give results. Faradic examination was only performed on some of the patients and it is therefore disregarded here. None of the patients were examined by electromyography. Without wishing to detract from the diagnostic value of these two methods, the later in particular, it seems that in practice the decision as to what line of treatment to adopt can

be made on the basis of observation If nerve function has not appeared at 3 months from the onset, then recourse must be had to operation

Several techniques of operation were used In 12 cases mastoidectomy was dispensed with, in the rest it was performed As far as the ultimate result is concerned, mastoidectomy was not found to be of avail This being so, and taking into account that space is limited when working in the area of the stylomastoid foramen through an endaural approach, it seems the best method to perform the operation through a retroauricular incision following in other respects the technique of O Meurman

In about 60 per cent of all cases the facial nerve was found to be pathological in appearance In cases where the nerve canal appeared normal throughout (total number 20) there was a distinct tendency for the entire nerve to be damaged Stenosis in the lower end of the nerve canal (3 cases of bony and 7 of cicatricial stenosis) caused chiefly changes in the vertical portion of the nerve, more infrequently in the whole nerve Although there were only 4 cases of capsular defect, even these showed a tendency to injury of the horizontal portion and of the entire nerve The entire nerve here refers to the exposed part

If the preoperative duration of disease did not exceed 3 months, the incidence of complete recoveries was 16 7 per cent A good results was obtained in 50 per cent, which figure includes the complete recoveries Recovery of facial function was moderately good in 66 7 per cent of the cases

Comparison of the degree of recovery of the individual branches shows that, in the series studied (30 cases) the 1st branch recovered good function in 53 3 per cent, the 2nd branch in 90 0 per cent, and the 3rd branch in 70 0 per cent Thus, recovery of the respective branches can be expressed approximately by the ratio 5 9 7

There was no correlation whatever between pain at the initial stage (12 cases) and the ultimate result In cases in which the palsy followed immediately upon exposure to cold, the average result of operation was definitely better than in those with spontaneous onset

ZUSAMMENFASSUNG

Die Untersuchung betrifft 34 operierte Falle von Bell'scher Fazialislahmung Rontgenologisch konnten keine pathologischen Veranderungen nachgewiesen werden Die Dekompressionsoperation des Nervs muss spatestens 3 Monate nach der Erkrankung duchgefuhrt werden Die Mastoidektomie hat sich vom Standpunkt des Endresultats als zwecklos erwiesen In etwa 60 % wurden pathologische Veranderungen im Nerv festgestellt In den Fallen mit Kapseldefecten bestand eine Tendenz zu Veranderungen im horizontalen Abschnitt des Nervs wahrend wieder in denjenigen Fallen, wo das *Foramen stylomastoideum* verengt war eine Tendenz zu Veranderungen im vertikalen Teil bestand Vollige Heilung wurde in 16 7 % erzielt und ein gutes Resultat in 50 % Die Heilung war in den verschiedenen Asten des Nervs nicht gleich Am besten heilte der Augen und am schlechtesten der Stirnzweig

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TRAUMATIC BONE CYSTS IN THE LOWER JAW

By

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There has been a lot of discussion about the traumatic bone cysts The etiology is uncertain and the classification therefore varying Accordingly they have been given different names such as traumatic, hemorrhagic and solitary cysts, or even simply "bone cavities" since they have no real cyst capsule

A characteristic is that they appear exclusively in young patients, usually 10—20 years of age According to the literature they seem to be comparatively rare At the Dept of Otology, Karolinska Hospital, however, 6 typical cases have been treated in the last years

The general clinical and roentgenological picture is described, the therapy discussed and the importance of a correct diagnosis underlined

THE DEPENDENCE OF CORNEO RETINAL POTENTIAL UPON ILLUMINATION

By

C V Munthe Fog

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The work has been carried out with support from Statens almindelige Videnskabsfond

Electronystagmography (E N G) is based on the difference in potential between the cornea and the retina which was demonstrated by du Bois Reymond in 1849

This potential occurs in the retina, the eye therefore functions as a dipole in which the cornea is positive and the fundus negative Schott (1922) was the first to succeed in recording a nystagmus reaction by electrical means

This means of registering nystagmus has gradually become more and more widely used, and articles on the subject of E N G now appear in nearly every issue of the otological journals, but in spite of this, very few investigations into the variation of the corneo retinal potential with illumination have been published

Aschan & Bergstedt (1955) and Aschan et al (1956) found no difference between the calibration with full illumination, and in the dark Henriksson (1955) was similarly unable to find any significant difference between calibration in the light and after dark adaptation, his investigations, however, were carried out after only 5 minutes dark adaptation

Miles (1940) measured the potential difference between the retina and cornea directly and obtained an average of 110 ± 30 μv in 33 young men After dark adaptation the potential difference fell to 88 ± 20 μv in the course of 10 minutes, only to rise to 126 ± 40 μv after 5 minutes illumination

Doesschate & Doesschate (1956) found that on dark adaptation the potential fell to a minimum and then rose again to reach approximately 90 % of its original value

Hamersma and Jongkees (1957) found a fall of about 10 % in the course of 5 minutes if the subject of the experiment closed his eyes, the experiments being carried out in a half dark room In Hamersma's nystagmographic investigations into caloric tests the subjects were dark adapted for 30 minutes before the calibration, he frequently repeated the calibration between experiments and by this means found only a slight fall in the corneo retinal potential

Kris (1958) found that during constant illumination the corneo retinal potential rose from 100 μv to approximately 175 μv, and thereafter fell to 60 μv In a series of 6 subjects she found that the swinging in potential lasted for up to one hour after the alteration in illumination

As there is thus some discrepancy between the results obtained by the various

CHANGES IN EYE POTENTIAL LEVEL* DURING ADAPTATION SUCCESSIVELY TO (a) STRONG ILLUMINATION, (b) DARKNESS & (c) MODERATE ILLUMINATION

(From Kris, C Nature Vol 182 pp 1027—1028 Oct 11th, 1958 Corneo Fundal Potential Variations during Light and Dark Adaptation) SUBJECT RS

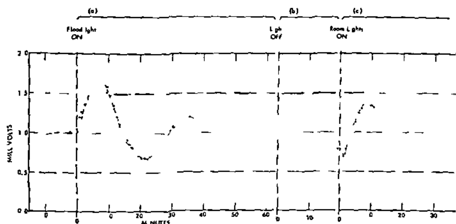


Fig 1

SCALES

* Ordinates *millivolts* change in potential across electrode-pair (recorded on Channel B) lateral and mesial to left eye, produced by standard 60° horizontal fixation shifts

Abscissa *minutes* after light was turned ON (a) & (c) or light was turned OFF (b)

** Approx 40 foot candles

*** Approx 2 foot-candles

investigators in their investigations into the alterations of corneo-retinal potential, I have investigated the dependence of this potential upon illumination in 20 subjects

The registration has been carried out using a Kaiser electroencephalograph, the time constant used has been one second

The electrodes are placed bitemporally near the external canthus, and the subject is connected to earth via the lobe of the right ear A fourth electrode is placed on the nose between the eyes so that the movements of each eye can be registered individually, simultaneous with the bitemporal registration The alterations in potential for the two eyes were, however, found to parallel the alterations in the bitemporal leads, and only the latter will therefore be referred to here

3 31 m in front of the subject is placed a horizontal rod with 2 small balls which are placed at a distance of 58 cm from one another, so that the subject makes an eye movement of 10° in moving the gaze from one to the other The difference in potential between the electrodes which results from this movement is amplified in the electroencephalograph and recorded by the writing pens

The calibration is carried out in dim light, so that the subject is able to see the two balls sufficiently clearly to carry out the 10° eye movement with certainty

To produce "absolute darkness' a pair of tightly fitting metal spectacles are placed on the subject, so that all light impressions are excluded

In "direct lighting" a 40 watt table lamp is placed at a distance of 50 cm from the subject, shining directly into his face

Alterations in corneo retinal potential will show themselves in that one will not obtain equal differences in voltage from one time to the next on calibration of the 10° eye movement An increase of corneo retinal potential will give greater differences in voltage, a reduction, smaller The electrode resistance has been measured in many experiments and found to be constant, it is generally about 5 kilo ohms

Experiments have been carried out on 5 subjects who had not previously been dark-adapted As the investigations were carried out during the spring and early summer, these subjects had been exposed to greatly varied light intensities immediately before the investigation In the cases of 3 of the subjects the potential was found to be more or less constant, these subjects had presumably only been exposed to weak illumination in the period before the investigation, whilst the remaining 2 showed a clear fall in potential when they came into absolute darkness In all cases it was found that the potential rose with illumination

After this, 5 other subjects were dark adapted by letting them wear green celluloid spectacles for 30 minutes before the experiment The spectacles allowed the passage of 0 90 % of the visible spectrum Despite this there was a clear fall in potential in 4 cases when they came into absolute darkness

In all experiments there was a considerable rise in potential with illumination, but with continued, constant illumination the potential fell again, even reaching a value below the original If after this the subjects came into absolute darkness, a further fall in corneo retinal potential was observed

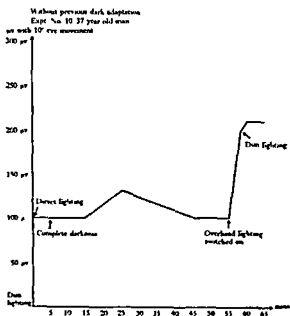


Fig 2.

The most interesting observation in this experimential series was that the corneo-retinal potential began to swing after strong illumination, and that about 30 minutes passed before it became relatively constant, even when the subject was in absolute darkness

These curves are very reminiscent of that of Kris (see figure 1)

Thus it was clear that the above-described spectacles could not bring the corneo retinal potential "into balance", and experiments were therefore made

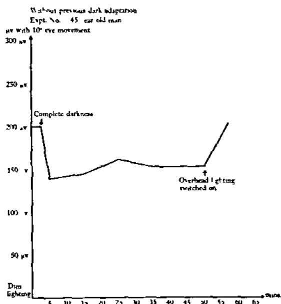


Fig 3

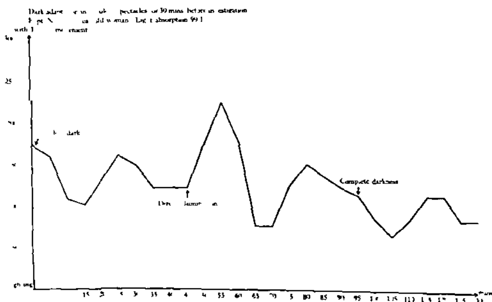


Fig 4

using a pair of tightly fitting, dark, green-tinted sunglasses, which permitted the passage of only 0.06 % of the visible spectrum. (The same spectacle-glass is used by oxy-acetylene welders.) Using these spectacles 10 subjects were dark-adapted for 30 minutes before the investigation, and in 9 of these the potentiil

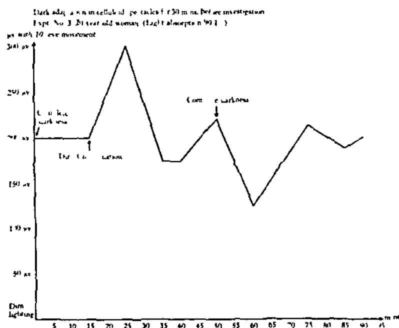


Fig 5

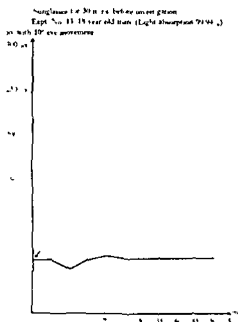


Fig 6

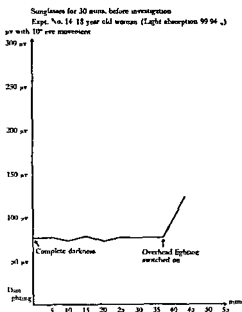


Fig 7

was found to be constant (see, for example, figures 6—7 & 8), but in one subject the potential was found to fall for 50 minutes (figure 9)

From the investigations described above one can therefore conclude that patients must be dark-adapted for about 30 minutes before they come to E N G if one wishes to measure the maximum eye-speed or the total amplitude. Even after 30 minutes dark-adaptation there are occasional subjects who have not

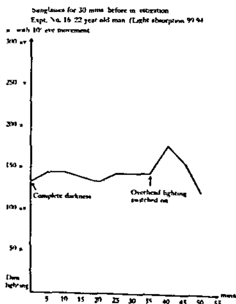


Fig 8

obtained a constant corneo-retinal potential, and it is therefore insufficient to be content with a single calibration, the calibration should be undertaken before each test If the eye is subjected to light the potential begins to swing, and if an investigation of optokinetic nystagmus is included, it should therefore be the last test made

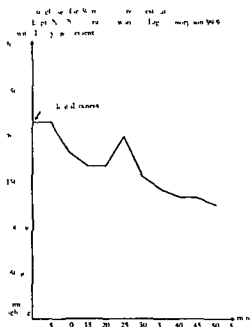


Fig. 9

SUMMARY

The dependence of the corneo-retinal potential upon illumination has been investigated in 20 subjects It was found that in the majority of cases the potential first became constant after 30 minutes dark adaption

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MECHANICS IN HIATAL INCOMPETENCE

By

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Abstract

Observations made in model experiments and subsequent clinical examinations have shown that *the viscosity and density (g/cm³) of the gastric contents influence the gastro-oesophageal closure* mechanism and that these properties must be considered in the investigation and treatment of hiatus hernia and gastro-oesophageal reflux

Though the closure mechanism at the gastro-oesophageal junction is not yet completely understood, certain physical factors of significance in the investigation of the closure mechanism are demonstrable by a 16 mm film[1]

The stomach is normally surrounded by mobile or loosely anchored organs of the same density (/cm³) as water Ordinary gastric contents are also of the same density as water with the result that the hydrostatic pressure normally acting on the inner surface of the stomach wall is the same as that acting on the outer wall

The contrast media conventionally used in the examination of the oesophagus and the stomach are much heavier than water Such contrast media therefore affect the shape and the function of the stomach and interfere with the closure mechanism at the gastro-oseophageal junction In an attempt to study the behaviour of the stomach with gastric contents of ordinary density an entirely new type of contrast medium was prepared The effect of the density of the gastric contents on the behaviour of the stomach is exemplified in model experiments and in cine roentgenography

As shown in the model experiments, intragastric an extragastric gas can influence the closure mechanism between the oesophagus and the stomach

The model experiments also show that the tendency to reflux can be reduced to a minimum by increasing the viscosity of the gastric contents In an attempt to utilize this observation in the medicinal treatment of gastro-oesophageal reflux and hiatus hernia a search was made for a non toxic substance of low density and viscous as long as it is in the stomach but readily soluble in the intestine

Various preparations were tried The best results were obtained with sodium alginate alginic acid Sodium alginate is readily soluble in neutral environments *In acid environments alginic acid precipitated with the formation of a gel* in neutral environments the gel is broken down with the formation of readily soluble sodium alginate In other words the preparation is viscous only as long as it is in the stomach and is readily soluble in the intestine To secure the best effect of treatment, the preparation is given as a carbon dioxide foam When

[1] The film shown at the congress is available on request

swallowed the light mixture is propelled down the oesophagus by peristalsis, after which it accumulates in the upper part of the stomach, and in the presence of a hernia, partly in the herniated part of the stomach On contact with the acid gastric contents, a supernatant layer of gel forms across the surface of the gastric contents The carbon dioxide gradually disappears, the density of the preparation increases, and the mixture is gradually transported to the intestine As long as the viscous suspension is accumulated in the region of the cardia, it counteracts regurgitation of acid gastric contents into the oesophagus The viscous suspension exerts this barrier effect not only when the subject is in standing position but also when he is lying In order to neutralize acid gastric contents that might nevertheless be regurgitated, conventional antacids are incorporated in the preparation

In cooperation with Ferring AB, Malmo, Sweden a powder (Gaviscon) was prepared This powder consisted of colloidal aluminium hydroxide, magnesium trisilicate, alginic acid and sodium bicarbonate Water is added to the powder before use

During the last 6 or 7 months some 50 patients have been treated with Gaviscon Most of these patients have verified hiatus hernia, some had been undergone gastro oesophagostomy, and some had diffuse dyspeptic symptoms without definitely demonstrable hiatus hernia or objectively demonstrable pathologic gastro oesophageal reflux The patients have been re-examined at fairly short intervals In some cases this follow up included repeated oesophagoscopy The results of treatment in patients with verified hernia as well as in those who had undergone gastro-oesophagostomy were invariably good No improvement has been noted in some of those patients with diffuse dyspeptic symptoms but without verified hiatus hernia or gastro-oesophageal reflux

The preparation Gaviscon appears to be a useful newcomer in the conservative treatment of hiatus hernia and gastro oesophageal reflux and may help to reduce the frequency of operations and of complications of oesophagitis

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ELECTRON MICROSCOPICAL OBSERVATIONS ON HYPER-KERATINIZATION IN ORAL MUCOSA

By

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The epithelium in the oral mucosa can be devided into certain regions with regards to the stages of keratinization Thus, the normal mucosa is not keratinized within the bottom of the oral cavity, in the vestibulum oris and on the lower side of the tongue, whereas an *increasing degree of keratinization is found in* the mucous membrane of the gingiva, on the upper surface of the tongue, and on the hard palate (Orban 1953, Weinman 1940)

Epithelium which is normally not keratinized might produce keratin under effect of mechanical, chemical, thermal or galvanic stimuli In certain cases pathological keratinization is found without such evident causes of the changes

This hyperkeratinization or parakeratosis provides the common histopathological background to the clinical picture of leukoplakia Although the word leukoplakia is hardly well defined clinically, the usual white spot in the mucous membrane described as a leukoplakia appears in the microscope as an area with hyperplastic stratified squamous epithelium with varying degree of hyperkeratosis (Pindborg 1962, Renstrup 1958, Waldron and Schafer 1960) The fact that cancer is sometimes observed within advanced leukoplakias justifies a careful analysis of the process of keratinization in the oral cavity (Renstrup 1958, Waldron and Shafer 1960, Hertz 1961, Shafer and Waldron 1961)

MATERIAL AND METHODS

Normal specimens from the vestibulum oris, palate and gingiva have been compared with specimens from leukoplakias within the same areas

Electron Microscopy Pieces of tissue were taken with a punch or a knife, fixed in 1 % buffered isotone osmium tetroxide solution (Rhodin 1954) embedded in Epon or Vestopal, sectioned with glass knives on a LKB Ultrotom, stained with phosphotungstic acid or/and uranyl acetate and studied in a Siemens Elmiskop I

Light Microscopy Pieces from neighbouring areas were fixed in buffered neutral 7 % formol and embedded in paraffin wax

RESULTS

Normal Structure The normal not keratinized epithelium in the oral mucosa is a stratified squamos cell epithelium with three distinct layers, stratum basale, stratum spinosum and stratum superficiale

The basal cells form a few rows of irregular cubical cells which appear denser

[1] Supported by the Swedish Cancer Research Foundation

swallowed the light mixture is propelled down the oesophagus by peristalsis, after which it accumulates in the upper part of the stomach, and in the presence of a hernia, partly in the herniated part of the stomach On contact with the acid gastric contents, a supernatant layer of gel forms across the surface of the gastric contents The carbon dioxide gradually disappears, the density of the preparation increases, and the mixture is gradually transported to the intestine As long as the viscous suspension is accumulated in the region of the cardia, it counteracts regurgitation of acid gastric contents into the oesophagus The viscous suspension exerts this barrier effect not only when the subject is in standing position but also when he is lying In order to neutralize acid gastric contents that might nevertheless be regurgitated, conventional antacids are incorporated in the preparation

In cooperation with Ferring AB, Malmo, Sweden, a powder (Gaviscon) was prepared This powder consisted of colloidal aluminium hydroxide, magnesium trisilicate, alginic acid, and sodium bicarbonate Water is added to the powder before use

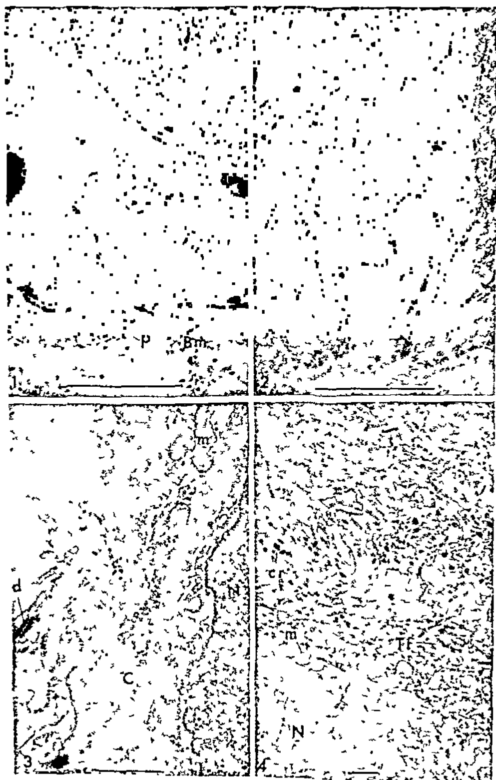
During the last 6 or 7 months some 50 patients have been treated with Gaviscon Most of these patients have verified hiatus hernia, some had been undergone gastro-oesophagostomy, and some had diffuse dyspeptic symptoms without definitely demonstrable hiatus hernia or objectively demonstrable pathologic gastro oesophageal reflux The patients have been re-examined at fairly short intervals In some cases this follow-up included repeated oesophagoscopy The results of treatment in patients with verified hernia as well as in those who had undergone gastro oesophagostomy were invariably good No improvement has been noted in some of those patients with diffuse dyspeptic symptoms but without verified hiatus hernia or gastro oesophageal reflux

The preparation Gaviscon appears to be a useful newcomer in the conservative treatment of hiatus hernia and gastro oesophageal reflux and may help to reduce the frequency of operations and of complications of oesophagitis

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Pl I



in the picture than the cells closer to the surface The basal cells are basophilic because of high content of ribonucleic acid

The cells within the stratum spinosum are irregular polygonal cells with a large number of prickles on the surface Neighbouring cells contact each others through these prickles, and at the point of contact between two prickles is found a dense area called the desmosome The prickles become shorter closer to the sur face of the epithelium, the cells become more flattened and the desmosomes apear different in structure

In the electron microscope a large number of details appear within the cells (Sognnaess et al 1956, Sognnaess et al 1958, Themann 1958, Albright 1960, Zelickson 1961, Zelickson et al 1961 and Zelickson et al 1962) and through combination of histochemical and electron microscopical observations of cells and cell structures, several informations will be achieved about the functional status of the cells

The connective tissue layer below the basal cells is delimited from the plasma membrane of the basal cells by a 2500 A thick homogeneous basement membrane (Fasske 1959) A zone of praecollagenous cross striped fibres appears below the basement membrane These fibers are anchored in the basement membrane and form a layer of loosely arranged fibers about 1 microne long going mainly perpendicular to the membrane Below these fibres are found around 2000 A thick collagenous fibres with normal band striation with typical periodicity These three layers form together the zone which appears as a basement membrane in the light microscope

The basal plasma membrane of the *basal cells* shows a number of half desmo somes These structures are formed by several dense layers inside the plasma membrane which is also split into several layers within the desmosome The cytoplasm of the normal basal cells within not keratinized epithelium contains only scattered tonofibrils evenly distributed throughout the cytoplasm The relative density of the cytoplasm as observed in the light microscope is due to even distribution of a large number of granules 150—300 A in diameter, the socalled ribosomes Some of the ribosomes appear in groups or connected to the membrane surrounding vacuoles in the cytoplasm These ribosomes contain ribonucleoproteins and are considered to serve as centre for protein synthesis in the cytoplasm (Fig 1)

→

Fig 1 Normal human basal cell from non keratinizing check epithelium Tonofilaments (tf) and ribosomes are evenly distributed in the cytoplasm Half desmosomes (d) attach the basal plasma membrane to the basement membrane (Bm) which is in close contact with the zone of praecollagen fibres (p) Mitochondria (m) often contain a dense body

Fig 2 Basal cell from oral vestibulum leukoplakia with bundles of tonofibrils (Tf) and ribosomes aggregated in small heaps (r)

Fig 3 Normal buccal spinous cell Cytoplasm shows evenly distributed tonofilaments and ribo somes with tendency to form aggregates Mitochondria (m) are seen close to the nucleus (N) in the area of contact between the cells some desmosomes are noted (d)

Fig 4 Spinous cells of oral leukoplakia Tonofibrils (Tf) in characteristic bundles dominating the cytoplasm Mitochondria (m) close to the nucleus (N) In the peripheral cytoplasm are found small bodies supposed to be crystals of phospholipids (Cr) Compare fig 5

conditions Development of leukoplakia in non keratinized areas of the oral mucosa means that considerable changes take place in all layers of the epithelium The fine structure of the normal and pathologically keratinized epithelium is described and discussed

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In specimens with parakeratosis the keratohyalin granules are not observed There is, however, lamellated granules in the peripheral layers of the stratum spinosum of the same type as those described above

In *stratum spinosum* the cells are transformed into the irregularly shaped prickle cells which form the thickest layer within the epithelium The complicated layering of the desmosomes appears clearly in this stratum (Fig 5) The tonofibrils increase slightly in number but they are evenly distributed within the cell cytoplasm and no thick bundles are observed The mitochondria, which appear as rod shaped bodies with typical internal membrane structure in the basal cell layer, loose their internal membranes and swell in the prickle cells The nucleus degenerates, the cytoplasm turns into a loose web like fibrillar structure with most of the fibrils parallel to the cell surface The ribosomes tend to form dense conglomerates Closer to the surface the cell protrusions become thicker and shorter, the cells become more flattened in shape and the desmosomes loose some of their layers There are no keratohyalin granules in the stratum spinosum cells of the normal non keratinized epithelium (Fig 7)

DISCUSSION

The characteristic structure of the various cell layers in leukoplakia as described in the present paper differs little from that of the normally keratinized epithelium in the palate or gingiva (Zelickson 1960) However, leukoplakia from different patients show varying degree of hyperplasia and of keratinization It is thus possible to study various stages of the process of keratinization in the oral mucosa under normal and pathological conditions

Very significant changes appear in the various cell layers of the oral mucosa during pathological keratinization when the normal and pathological materials are compared The process of keratinization means that a great amount of proteins are transformed from one type to another The keratohyalin granules seem to form intermediate stages under the transformation of tonofibrils into keratin fibrils It seems as if the formation of keratohyalin granules takes place in close relation to conglomerates of ribosomes in contact with tonofibril bundles (Brody, 1960) Hypothetically the ribosomes could serve as centers for the synthesis of keratin of tonofibrils and energy rich bonds

Jarret (1960) produced parakeratosis in the skin of mouse tail by continuous pressure He demonstrated increase in the content of phospholipids in the epithelium and concluded that energy needed for the keratinization was taken from energy rich bonds in the phospholipids It seems possible that the crystal like bodies observed in the stratum spinosum cells of keratinizing epithelium in leukoplakias are crystals of phospholipids needed for this process

SUMMARY

Human oral mucosa was studied with light and electron microscope with special regard to the process of keratinization under normal and pathological

tensor muscle as well, causing an objective tinnitus substantiated by an audible clicking noise.

Four such cases are recorded and will be shown on this film

Case 1

Woman, 58 years of age, was in 1960 admitted to the neurological department She was complaining of a ticking sound in the left ear, and ordinary tinnitus of a blowing character in the right ear, spells of dizziness which could last for about 1½ hours, and a pressing sort of headache felt most strongly on the left side of the head She also felt clonic contractions of the palate

As to the *case history* she had (at the age of 36) in 1938 what she called "a nervous breakdown" during a period of strainy work After this she had at intervals streaming sensations to the head In 1946 (at the age of 44) she got married, and in 1952 she for the first time noticed tinnitus and the characteristic ticking sound in the left ear — As to the *dental state* she got a full upper denture in 1948 and had at that time lost all her molars and premolars in the lower jaw, so she had no molar support — The following year, in 1949, she got troublesome headache which had the character of migraine A few years afterwards, in 1952, she got symptoms from the ears, consisting of subjective and objective tinnitus So in 1955 she had her lower teeth pulled out and got a full upper and lower denture At the time of admission to hospital the dentures were found in sufficient with a low faulty bite. Due to these circumstances she had pain and tenderness of both mandibular joints, subluxation on the left side and deterioration of headpains and ear symptoms, including diminished hearing and dizziness

The clicking in the left ear was synchronous with clonic contractions of the soft palate on same side The sound varied in intensity and there could be quiet periods in which the contractions were absent. But even so the left palatal arch was found to stand at a higher level than on the right side She was able to start the clonic movements voluntarily by contraction of the masticators and the muscles of the throat The tympanic membrane could also be seen vibrating synchronous with the ticking sound

The sound was recorded by placing a microphone at the left ear By a special arrangement with an acoustic measuring bridge in the left ear, rhythmic variations were found in the impedance of the sound-conducting system in the middle ear This is interpreted as being due to spontaneous activity of the tensor tympani muscle Each contraction of the muscle is marked by a spike on the recording a steep rise and a curved fall, synchronous with the ticking

By asking the patient to keep her breath, the contractions came to a standstill for the time being When she commenced breathing spontaneous activity could again be observed

When she relaxed the jaw, the concentrations abated, and by opening the mouth wide which means fully relaxation of the biting muscles as well as the tensor muscles, the contractions went off record This clearly demonstrates the reciprocal innervation of the groups of muscles for opening and closing of the jaw, the tympanic and palatine tensor muscles being synergetic with the closers

CLICKING EAR AND PHARYNGEAL TIC ASSOCIATED WITH FUNCTIONAL DISTURBANCES OF THE JAW

By

Hilmar Myrhaug

Dental Clinic Haukeland Hospital, Bergen, Norway

Bite deformities which lead to functional disturbances of the jaw is a known cause of tinnitus aurium or noises in the ear This sensation of sound in the ear has no adequate stimulus from outside It seems frequently to originate from autogenous vibrations of the sound conducting structures in the middle ear Those vibrations are able to stimulate the sense organs in the inner ear in a similar manner as a sound wave striking at the tympanic membrane The ordinary tinnitus is percepted by the patient only and is of the *subjective* type But in rare instances the sound can also be heard by a second person and is then called *objective tinnitus* This entotic sound has a clicking character like the ticking of a clock or the crackling of an electric spark It may follow a certain rhythm, but has no relation to pulse or respiration or movement of the mandible

There are few cases of this kind in the literature, but in the publications on the subject there have been done no competent examination of the teeth and the dental state of the patients But some references of trauma to the jaw are mentioned, and this lead us to think of the anatomical and functional relationship between the ear and the jaws, as the middle ear bones and muscles are partly considered to be jaw structures passed over to the service of hearing

The sound-conducting apparatus of the middle ear, consisting of the chain of ear bones, the auditory ossicles malleus, incus and stapes, and the appertinent muscles, the tensor tympani and the stapedial muscle, have a rather labile suspension This is due to the tendons, the joint capsules and the ligament of the oval window made up of *elastic* fibres, which is exceptional compared to other joints — The middle ear muscles take an important part in keeping the stability of this elastic system The larger of them, the tensor tympanic muscle, is supplied by the trigeminus, while the smaller stapedial muscle is innervated from the facial nerve Even though the middle ear muscles are found to be fully co ordinated in action, the stability of the sound conducting apparatus become easily disturbed This seems to happen when spasm or a state of stress is affecting the muscles innervated by the trigeminal nerve, primarily the masticators and second arily the tensor tympani and palatine tensor muscles Those two tensor muscles are closely connected to each other by an intermuscular tendon and may even have muscle fibres in common In the first place the tensor tympani muscle seems to react to stress conditions of the masticators by clonic contractions (myorhythmia), probably as a result of fatigue or exhaustion Autogenous vibrations of the middle ear system is explained on this basis and the sensation of subjective tinnitus likewise More seldom clonic contractions appear in the palatine

pain through the head She had a habit of pressing the jaws when she was busy occupied during working hours — No impairment of hearing was found

In this case the synchronous palatal movements could not be clearly demonstrated The left palatal arch was found to stand at a higher level than the right one The crackling sound in the ears as well as the palatal movements were mostly abolished by wide opening of the mouth This is due to relaxation of the masticating muscles (the closers) as well as the palatal and tympanic tensor muscles when the mouth is opened wide When the mouth was kept shut, volleys of spontaneous activity of the tympanic tensor muscle could therefore be demonstrated on the acoustic measuring bridge and recorded on the diagram

Case 4

The younger sister is 17 In this case there is also a marked asymmetry of the face On opening the mouth wide there is a deviation and zig zag-movement of the jaw The condylar head of the jaw joints are seen to pass into a position of subluxation by extreme opening She had to start an orthodontic treatment at the age of 11, and after this event, she noticed a clicking sound in the ears, most clearly percepted on the right side where it also was recorded

For several years, from elementary school and upwards, she had migrainous headache alternating from one side to the other, spreading to the neck and shoulders Often she wakes up in the morning with headache which may get worse during the day when she also has vertigo, vomiting and flares and may have to go home from school Sometimes she also notice popping in the ears and the clicking differs a lot Is it worse when the jaws are strained, e g during dental treatment The clicking is percepted only in conjunction with movement of the soft palate

The clicking sound was registered last summer (1962) A checkup in March 1963 showed no spontaneous activity of the middle ear muscles on the acoustic measuring bridge, and the clicking sound is now only sporadic This may be due to the bite now being stabilized after orthodontic interference

DISCUSSION

Gundersen to Myrhaug

The 4 cases demonstrated in Dr Myrhaug s film all had nervous tics with spontaneous movements of the soft palate The tensor veli muscle contracts and pumps air into the middle ear The impedance changes measured here may bee due to changes in the air pressure and not to reflexes of the middle ear muscles

Case 2

Man, 37 years of age He was in 1960 admitted to the surgical department with a badly fractured leg after falling into the dock-yard He was operated on the day of admission and after awakening from the general anesthesia, he noticed popping sensations in the left ear and the following day he had tinnitus Later on he complained of pain in the ear, neuralgic pains to the left temple region and stabbing pain in the head The pain started behind the left ear No definite changes of the ear drum could be found The dental state was quite good, but as he had lost some of the molars, there was a sliding movement by articulation as a wisdom-tooth in the left upper jaw and other posterior teeth had a forward inclination He had a comparatively deep overbite on the front teeth — He stayed in hospital for 3 months During the training programme in moving the ankle, which was very painful, he had the habit of clenching the teeth

During this period he had a terrible pain in the left ear and noticed a crackling sound in the head, terminating with a sharp click in the ears

Simultaneously there could be observed clonic contractions of the soft palate, the left palatal arch being more contracted than the right one No movement of the tympanic membrane could be seen

By means of an acoustic measuring bridge in the left ear, rhythmic changes of the impedance could be recorded, the spikes being identical with those produced by contraction of the tensor tympani muscle

As in the first case, the contractions were abolished by wide opening of the mouth

No spontaneous activity was found in the right ear, while signs of contraction could be elicited by a jet of air to this ear These examples seem to demonstrate how mechanical stimulation and functional disturbances of the jaw may affect the trigeminus innervated muscles of the ear and bring about disorders of hearing and balance

Case 3

In the year 1962 there have been registered two other cases in this series They are two sisters who both were taking orthodontic treatment in order to correct a faulty bite

The elder of them, *case no 3*, is 20 years of age and she is here presented first There is a slight asymmetry of the face and at times she noticed cracking noises in the mandibular joints There was also some zig zaging of the jaw when opening wide

Since the age of 10 she had popping sensations in the ears, mostly on the right, alternating with a crackling sound ending with a click in the ear There was no tinnitus except for the crackling noises Sometimes there could be a continuous stream of crackling followed by a pause of a few seconds The noises could also be percepted by the examiner and was recorded as follows (Record)

She had also vertiginous sensations especially when she was tired and when turning and stooping The last 7—8 years she had a troublesome headache, located to the forehead above the eyes and at times she had a stinging, burning

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ELECTRONYSTAGMOGRAPHY

A discussion of its use and usefulness in
the study of clinical problems, physiology
and pharmacology of the vestibular system

by

L B W JONGKEES and A J PHILIPSZOON

INDEX

INTRODUCTION

1 *Description of apparatus*

The main aim of this paper is to demonstrate the outstanding value of electronystagmography as a diagnostic tool and the usefulness of this technique in vestibular research work

The first attempts to record eye movements were carried out with photographic or mechanical means We mention BERLIN (1891), BUYS (1909), OHM (1914), STRUYCKEN (1918), DOHLMAN (1925), KUILMAN (1931) and NAVIS (1938)

Later on electronystagmography was introduced which gives by far the best results

In the retina electric processes are always taking place, even in the dark, causing the retina to be charged negatively as against the cornea Hence the eye is to be considered as a dipole, the electrical axis of which coincides with the optical axis Any movement of the eye changes the field power in the region near the eye With the nystagmograph the eye movements are recorded via these changes in the field power (see Fig 1)

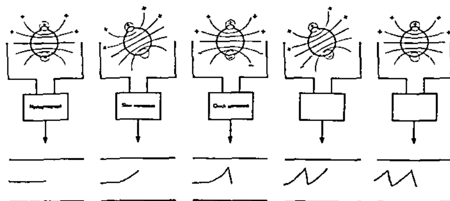


Fig 1 Recording of nystagmus The slow movement is directed towards the right and the quick movement towards the left

The existence of the above mentioned corneo-retinal potential difference was already described by DUBOIS REYMOND in 1849

Publications on electronystagmography appeared amongst others by SCHOTT

BOESEL (1952), HERTZ and RISKAER (1953), RUDING (1953), VAN EGMOND and TOLK (1954), HENRIKSSON (1955), ASCHAN, BERGSTEDT and STAHLE (1956), HAMERSMA (1957), PREBER (1958), STAHLE (1958), PHILIPSZOON (1959), HAKAS and KORNHUBER (1959), MAAS (1960), JONGKEES and PHILIPSZOON (1960),

HENNEBERT (1960), BERGSTEDT (1961), BOS (1962) ABOULKER, PIALOUX, NEVEU, BUTRUILLE and BOUCHET (1963), OOSTERVELD (1963)

To record the true position of the eye, a nystagmograph of the d c type should be used This means that it has to respond also to the d c component in the signal Instrumentally it is much simpler to construct an a c amplifier, which reacts essentially to variations in the input potential When an a c amplifier is used no difficulties arise from the electrodes For practical use in the clinic it is not easy to work with a d c amplifier as routine, because the caring for the electrodes is, even if possible, too time consuming This is the main reason why in routine clinical work in our opinion an a c amplifier should be used An a c amplifier follows a sudden step in the input signal rather accurately, but the output signal immediately begins to drift back to the equilibrium value (fig 2A)

In our apparatus the practical problems are solved in the following way

By the use of a special coupling network between the stages of the amplifier this response can be improved After a sudden step in the input signal the output remains for a short time (0 7 seconds) at its newly reached value, reaching the zero line in about 10 seconds (see Fig 2B) This expedient considerably improves the response to a square wave On the other hand, the recovery time of

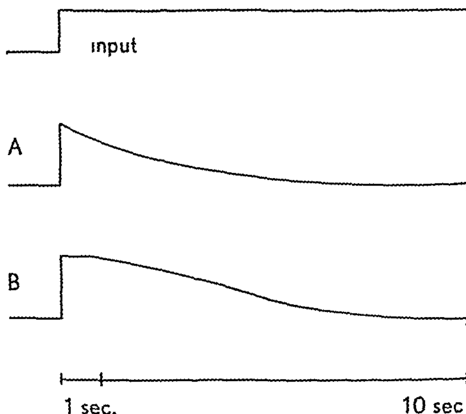


Fig 2. A Response characteristic of an amplifying system in which the response decreases immediately B Response characteristic of our nystagmograph showing a constant level for 0 7 seconds

the instrument is sufficiently short to allow difficulties due to drift to be avoided

Details of our coupling network are given in Fig 3 and 4

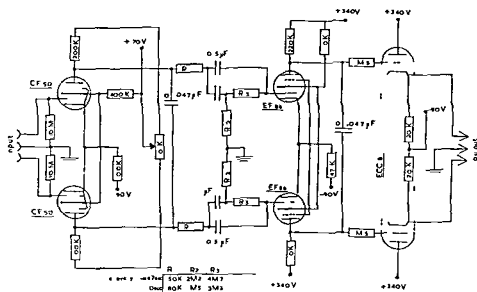


Fig 3 Circuit diagram of the A C amplifier

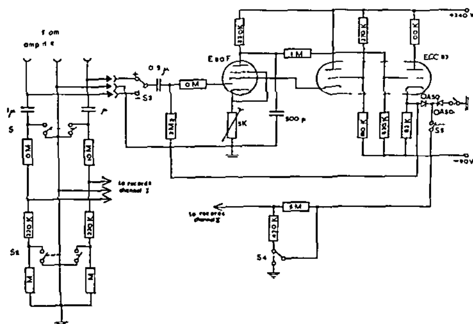


Fig 4 Circuit diagram of the derivation unit

Our nystagmograph * consists of alternating current amplifiers, from which the signal is led to a direct writing electrocardiograph (Elema Mingograph, Stockholm)

* Our apparatus was designed by E DE BOER PH D

The amplifiers are fed by a stabilizing unit. A similar system was used by ASCHAN, BERGSTEDT and STAHLE (1956) and by HENRIKSSON (1955, 1956).

We also have at our disposal a derivation unit for the recording of the eye speed of the slow phase according to HENRIKSSON (fig. 4).

The calculation of the eye speed of the slow phase can, of course, also be done directly from the normal recording. For this we have to calibrate the recordings of eye movements of the patient. We do this in the following way. We have the patient look at two white dots on the wall and shift his gaze from the one to the other, in such a way that the eyes move over 20 degrees. This proves to be a very easy way to measure the eye speed. For further details see fig. 5.

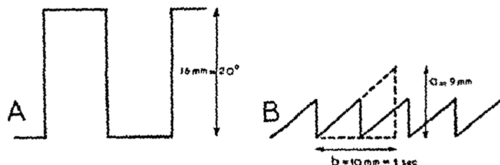


Fig. 5. Calculation of the speed of slow nystagmus phase.

A. Calibration 16 mm = 20°. B. Nystagmus.

The speed of the slow phase $= \frac{a}{b}$

We always choose b in such a way that b = 1 cm = 1 sec. (at a paper speed of 1 cm/sec.)
When a = 9 mm the speed of the slow phase is

$$s = \frac{a}{b} = 9\ \text{mm}/\text{sec} = \frac{9}{16} \times 20°/\text{sec} = 11°/\text{sec}$$

An apparatus similar to ours can easily be constructed from amplifiers commercially obtainable. A Tektronix power supply 127 with a Type E plug in unit, in which a filter is added for cutting the frequencies above 8 Herz gives highly satisfactory results. It is also possible to utilize the special coupling network, referred to above, in this preamplifier.

As electrodes we use three stainless steel disks, 8 mm in diameter, 2 mm thick, with concave surfaces. The cavities are filled up with electrode paste as used in electrocardiography.

Two electrodes are fixed with plaster on the skin of the temples, about 2 cm from the lateral canthus. The third electrode, serving as ground electrode, is fixed at the centre of the forehead. The electrodes are placed in such a way that an eye movement towards the left is recorded as a downward deviation on the paper and a movement to the right as an upward deviation. In this way only horizontal eye movements are recorded. If we want to record vertical eye movements the electrodes should be put above and below the eye. In this case an upward deviation represents an upward movement of the eye and a downward deviation a downward movement of the eye. As a matter of fact

it is impossible to record a purely rotatory nystagmus, because in this case the eye rotates round its electrical axis, in which way the axis of the dipole does not move with regard to the electrodes, in whatever place they should be fixed By means of electronystagmography it is not possible either to record eye movements in some categories of blind patients in whom no corneo retinal potential difference exists In these cases photo-electro-nystagmography might solve the problem (TOROK, GUILLEMIN and BARNOTHY, 1951; PFALTZ and RICHTER, 1956).

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2 *The evaluation of the corneo retinal potential difference (C R P) in rabbits*

In human beings it is very easy to calibrate eye movements We just let them look from a certain distance to two points on the wall alternately in such a way always the same eye movement is performed This is not possible in rabbits When we, however, want to do experiments in rabbits using electronystagmography it is still necessary to know something about the behaviour of the C R P For this reason we developed a method to calibrate the C R P in rabbits by means of passive eye movements (Philipszoon, 1959)

By always giving the same movement to the rabbit's eye and recording this movement, it ought to be possible, by measuring changes of the amplitude of the curve which show on the recording paper, to draw conclusions about changes in the C R P Thus, even if the absolute C R P is not measured, changes in the electrical charge of the eye can indeed be found

For this purpose the rabbit was fixed on a rabbit board, its head in a clamp The electrodes were put in front of and behind the eye in such a way that a movement to the right gave an upward deviation on the registration paper and vice versa

As electrodes for rabbits we used three injection needles (nr 20), which were insulated except for three millimeters from the point One of the needles was used as ground electrode, the two others serving to record changes in the field potential The latter two were put in the skin on either side of one eye and fixed with collodion The ground electrode was put in the skin over the middle of the head (fig 6)

After the cornea had been made insensitive with pantocaïne a thread was sutured with two or three stitches in the cornea (fig 7) One end of the thread was led via a small pulley to an electromagnetic relay, the other end was fastened to

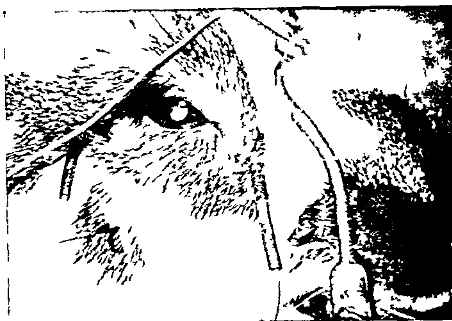


Fig. 6 Fixation of the electrodes in rabbits

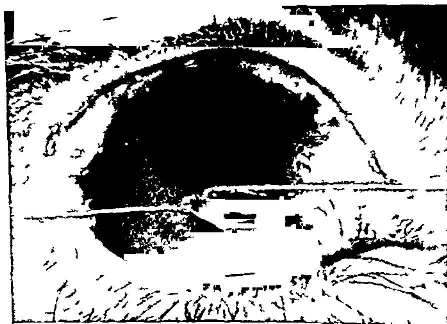


Fig. 7 Fixation of thread into the cornea

a small counterweight via another pulley (fig 8) Switching on of the current — that was given by an accumulator — caused the eye to be drawn forward Switching off made the counterweight draw the eye back to its original position In this way we could easily repeat the movement of the eye This movement was recorded on the paper and directly checked by fixing to the lever of the relay a thread, that was connected via a pulley to another counterweight The rotation of the latter pulley wheel was recorded on the second channel of the recording system (the Mingograf) The position of the axle of the pulley was linearly con

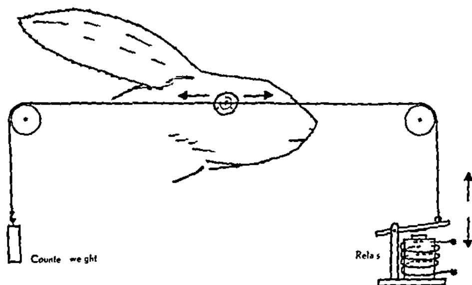


Fig 8 Scheme showing the measurement and assessment of the corneo-retinal potential difference

verted into a voltage by a potentiometer that was electrically a part of a Wheatstone bridge circuit

Any change in the amplitude of the eye movement recorded via the C.R P, not accompanied by a simultaneous change in the curve of the direct recording, can only be due to a change in the C R.P , as we always gave the same movement to the eye

We found that only very slight spontaneous changes in the C R P occur after a rabbit has been in the dark for half an hour or more For this purpose we measured in ten rabbits the C R P every five minutes for one hour and a half, starting immediately after they had been put in the dark During the first half hour, and especially during the first fifteen minutes, the C R P clearly decreased, to remain practically constant after the first half hour (fig 9)

In order to exclude an effect of pantocaine 0 5 per cent on the C R P we anaesthesised two rabbits completely with Nembutal We then measured the effect of the instillation of pantocaine 0 5 per cent in the eye on the C.R P There was no such effect

NOELL (1952) and HECK and PAPST (1957) also discribed methods to measure the C.R P but they are more complicated than ours

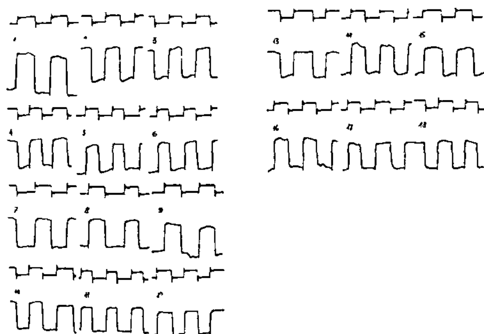


Fig 9 The corneo-retinal potential difference in a rabbit after it has been put in the dark, during one and a half hour, measured at intervals of 5 minutes The upper line represents the movements of the relay, the lower line the movements of the eye

A disadvantage of their methods is that they need manipulation of the eye muscles, which interferes with the blood supply of the eyebulb, because the vessels which supply the eyebulb are situated in the eyemuscles (POLYAK, 1957)

In order to check our experimental arrangement we treated rabbits with sodium iodate ($NaIO_3$) and other rabbits with sodium azide (NaN_3) Sodium iodate reduces the C R P by chemical destruction of the retina cells while sodium azide gives an enlargement of the C R P (NOELL, 1952, HECK and PAPST, 1957) Using our method we got indeed a reduction of the C.R P by injection of 0 3 g $NaIO_3$ into a vein of the ear We did not get a reduction of the C R P to zero as NOELL (1952) and HECK and PAPST (1957), unless we gave huge doses which caused the animal to die This is probably due to the fact that the above mentioned authors used for the measurement of the C R P methods in which the eyebulb and especially the eyemuscles are injured in such a way that little is to be needed to reduce the C R P to zero We easily succeeded to perform by an intraperitoneal injection of 20 mg NaN_3 the so called azide-effect (NOELL, 1952, HECK and PAPST, 1957) viz an increase of the C.R P (fig 10)

This method was also used to study the influence of dark adaptation on the corneo retinal potential difference in comparison with the electroretinogram HORSTEN, PHILIPSZOON and WINKELMAN, (1963) found that dark adaptation under the same conditions gave an increase of the amplitude of the retinogram and a decrease of the corneo retinal potential difference without any statistical correlation between the two items

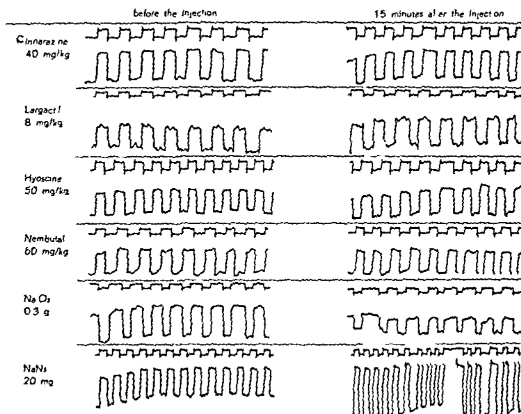


Fig. 10. The effect of some drugs upon the corneo-retinal potential difference; further legend see fig. 9.

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CHAPTER II

THE POSTURE TEST

1 *On spontaneous and positional nystagmus*

Since electronystagmography has been introduced into the clinic as a routine method for the examination of patients, several publications have appeared which differ in regard to opinion on the occurrence of spontaneous and/or positional nystagmus in normal subjects

Some authors give a rather high percentage, while other publications give a low frequency of this phenomenon in normal subjects STAHLE (1958) found no spontaneous or positional nystagmus in a material of 50 normal subjects BERGSTEDT (1961) found 9 times a nystagmus in 26 normal subjects JONGKEES, MAAS and PHILIPSZOON (1962) found in one subject out of a group of 85 normals, a spontaneous and positional nystagmus LANSBERG (1962) found in 8 per cent of a normal material of 230 subjects a spontaneous nystagmus VISSER (1962), studying spontaneous nystagmus in 30 normals and 66 patients, proposed a pathological limit for spontaneous nystagmus for a frequency greater than 0 5 beats per sec

The curves of more than 3000 patients gave us the impression that rather often a spontaneous or positional nystagmus does not indicate pathology It seems strange that we did not find a nystagmus in normals more frequently than the figure mentioned in an earlier publication (1 in 85 subjects) (JONGKEES, MAAS and PHILIPSZOON, 1962) After reviewing our old curves in normals, we found the following possible solution In most cases (dating from the beginning of a period of 7 years nystagmography in our clinic) the eye movements had only been recorded during a short time In the beginning we did not expect a high incidence in normal subjects This is the reason why we made the mistake to record the eye movements for a (too) short time only In patients complaining of vertigo, however, we expected to find nystagmus. This made us, unconsciously record longer tracings in patients

In order to solve this problem we decided to examine a completely new group of normal subjects (BOS, OOSTERVELD, PHILIPSZOON, VOZZA and ZELIG (1963)

We also tried to make new standards in order to decide whether a nystagmus, when present in the posture test, indicates vestibular pathology or not In the group of normals the eye movements were now recorded in each position for at least one minute We also examined, for comparison with the normal material, the curves of patients complaining of vertigo We took a group of patients with a perception deafness and a group of patients with a conduction deafness, both complaining of vertigo The two groups consisted of successive unselected patients visiting our department

Methods

We recorded the eye movements in the following positions sitting, supine position, on the left side, on the right side, prone position and head hanging position The eye movements were recorded while the eyes were closed The electrodes were fixed to the temples in order to record horizontal eye-movements In a great percentage (80%) of a normal material FLUUR and ERIKSSON (1961) found vertical spontaneous nystagmus For this reason we also recorded vertical eye movements in a number of our normal subjects In this case we placed electrodes above and below one of the eyes

From the curves we calculated 1) the maximum speed of the slow phase of the nystagmus, 2) the number of positions in which nystagmus was present and 3) the frequency

The maximum eye speed of the slow nystagmus phase was expressed in degrees per sec (°/sec) This could as stated in Chapter I easily be calculated from a calibration at the beginning of the test (fig 5)

RESULTS

Normal material We examined 149 healthy subjects from 18 to 54 years of age None of these subjects complained of vertigo 80 of them were younger than 25 years, 66 were between 25 and 40 years of age and 3 were older than 40 years 36 (24%) of these subjects showed a nystagmus in one or more positions Of these 36 subjects 16 showed a nystagmus in one position, only 9 had a nystagmus in two positions, 4 in three, 4 in four, 0 in five and 3 in all six positions

Thus 11 (8%) out of 149 normal subjects had a nystagmus in more than two positions and 7 subjects (5%) showed a nystagmus in more than three positions

As regards the maximum eye speed we found a speed greater than 6°/sec in 13 subjects (9% of all normals) In 5 subjects (3%) we found a speed greater than 7°/sec The highest speed we found in a normal subject was 11 °/sec

In 10 subjects (7%) we found a frequency more than 1 beat per second All these subjects had also an eye speed greater than 6°/sec or a nystagmus in more than two positions As this datum did not give any new information we did not extend the investigation of it in our patients

In 104 of our normal subjects we recorded vertical eye movements In 83 (80%) of them a vertical nystagmus was present In 74 we found an upward nystagmus, in 6 a downward nystagmus, in 3 a direction changing nystagmus and in 21 no vertical nystagmus In 58 of the subjects, showing vertical nystagmus, no horizontal nystagmus was present (fig 11) This confirms the findings of FLUUR and ERIKSSON (1961)

Perception deafness We performed the posture test in 145 patients with a perception deafness of one or both ears Of these patients 122 showed a nystagmus, 23 had no nystagmus 18 had a nystagmus in one position, 22 in two positions, 17 in three, 16 in four 19 in five and 30 in all six positions

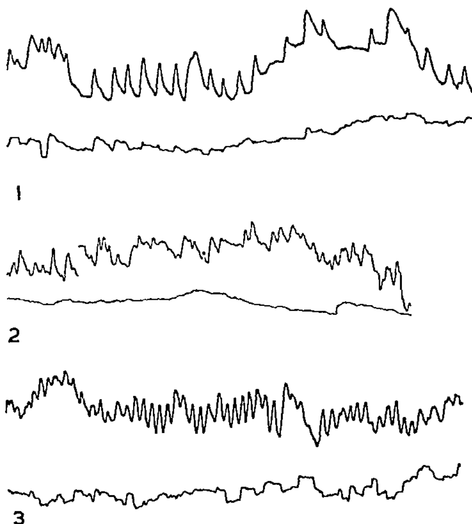


Fig 11 Three normal subjects showing a strong vertical nystagmus without horizontal nystagmus
The upper line represents the vertical, the lower line the horizontal eye movements

76 patients showed a nystagmus with a maximum speed of the slow phase higher than 6 °/sec and 69 of them had a speed higher than 7 °/sec The highest speed we found was 52 °/sec 20 patients had a nystagmus with a speed greater than 11 °/sec (the highest speed we found in a normal subject)

Conduction deafness We performed the posture test in 68 patients with a conduction deafness While 10 were negative, 58 had a nystagmus, 13 of them showed it in one position, 8 in two positions, 7 in three, 12 in four, 11 in five and 7 in alle six positions

45 had nystagmus with a maximum eye speed higher than 6 °/sec and 36 with a speed higher than 7 °/sec The highest speed we found was 40 °/sec 17 had a speed higher than 11°/sec

DISCUSSION

The fact that a nystagmus can be observed more frequently with the aid of nystagmography than by direct observation (with or without Frenzel's spectacles) is essential for the value of electronystagmography as a diagnostic tool JONGKEES, MAAS and PHILIPSZOON (1962) found with its aid 230 cases showing spontaneous positional nystagmus in 341 patients complaining of vertigo, while without nystagmography only in 52 of these patients a nystagmus was found (fig 12)

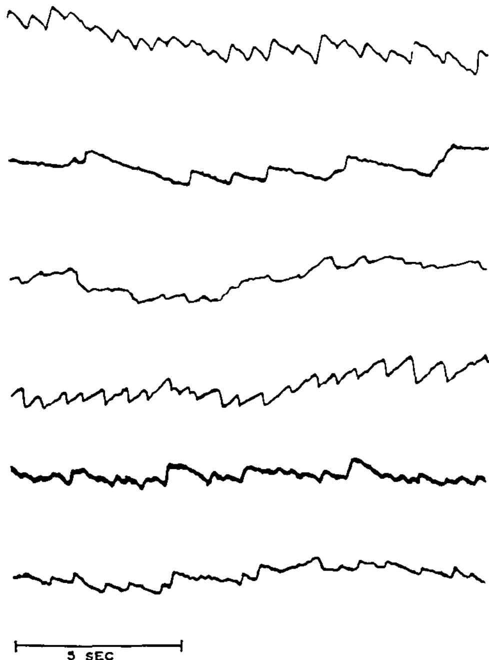


Fig 12 Specimens of nystagmus which were not observed visually

Thus by means of electronystagmography a nystagmus can be observed more frequently than by direct inspection of the eyes

The threshold of the human eye for the perception of a nystagmus is much higher by direct inspection than by means of electronystagmography

It appears that as a rule a nystagmus, the speed of the slow phase of which is less than 7 °/sec, cannot be observed even by a trained investigator, whereas by recording a nystagmus with a speed of 2 3 °/sec of the slow phase can still clearly be recognized Moreover, nystagmography has the advantage that in patients with closed eyes fixation is completely excluded, which is by no means the case during examination with Frenzel's spectacles as stressed by ASCHAN, BERGSTEDT and STAHLE (1956) (fig 13)

The aim of this part of our investigations is to find criteria, making it possible to judge whether a nystagmus is pathological or not



Fig 13 A Eyes open with Frenzel s spectacles no nystagmus B Eyes closed nystagmus

From our normal material we conclude that the threshold for pathology, as regards the number of positions in which a nystagmus is present, must be at a level of two or three positions, since only 8% of normal subjects have a nystagmus in more than two positions and 5% in more than three

As regards the maximum eye speed of the slow phase the pathological threshold will have to be put at about 6 or 7 °/sec, since 9% of our normal subjects have a speed higher than 6 °/sec and 3% higher than 7 °/sec

When we take into account both criteria simultaneously (maximum eye speed and the number of positive positions), we find that 18 (12%) of our 149 normal subjects have a nystagmus with a speed of the slow phase higher than 6 °/sec or show a nystagmus in more than two positions In the 145 dizzy patients with perception deafness 103 (71%) have a nystagmus with a speed higher than 6 °/sec or showing itself in more than two different positions In our 68 patients with perception deafness we found in 53 patients (78%) one of these two criteria to be positive

9 (6%) of our normal 149 subjects had a nystagmus with an eye speed higher than 7 °/sec or showing itself in more than three positions 86 (59%) of our patients with perception deafness and 40 (59%) of our patients with conduction deafness had a nystagmus with a higher speed than 7 °/sec or present in more than three positions

Of our 149 normal subjects 6 (4%) showed a nystagmus with a speed higher than 6 °/sec in more than two positions These two criteria were simultaneously positive in 53 patients (36%) with perception deafness and in 28 patients (41%) with conduction deafness

In our opinion we may draw the following conclusions. When in a patient a horizontal nystagmus is found with a higher speed than 6 °/sec or if it is present in more than two positions, it is probable that this nystagmus is pathological. When its speed is higher than 7°/sec or when it is present in more than three positions it is highly probable that this nystagmus is pathological. When we find a nystagmus with a speed higher than 6 °/sec in more than two positions, there is also a strong indication for pathology.

The performance of the posture test in combination with an audiogram simplifies the routine vestibular examination to a very great extent.

When audiogram and posture test (with the aid of electronystagmography) are performed, little new information is to be obtained from the caloric test (JONGKEES, MAAS and PHILIPSZOON, 1962). When in the caloric test we find a difference in excitability between both ears or a directional preponderance, we nearly always find a spontaneous or positional nystagmus in combination with a perception deafness accompanied by positive recruitment.

In a great many cases, therefore, the caloric test will give no new information. For this reason it is highly important to know the criteria for pathological spontaneous and positional nystagmus. (See Chapter III).

SUMMARY

The result of the posture test with the use of electronystagmography is described in patients and in normal subjects. They are examined in the following six positions: sitting, supine position, on the left side, on the right side, prone position and head hanging position. The eye movements are recorded while the eyes are closed. A group of 149 normal subjects is compared with 145 patients with perception deafness and 68 patients with conduction deafness.

When a horizontal nystagmus is found in more than two positions or when a nystagmus has a maximum eye speed of the slow phase higher than 7°/sec, this strongly indicates pathology. A vertical nystagmus, which is recorded electronystagmographically with closed eyes is not pathological since 80% of normal subjects show such a nystagmus.

By means of electronystagmography a spontaneous or positional nystagmus will be found over four times as frequently as by direct observation (with or without the aid of Frenzel's spectacles).

When audiogram and posture test (with the aid of electronystagmography) are performed little new information is to be obtained from the caloric test. This makes the routine clinical examination much simpler and less time consuming since the posture test as described by us takes very little time (about 10 minutes).

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2 *Identification of eye movements (nystagmus or no nystagmus)*

An obvious advantage of nystagmography over direct visual observation of eye movements, with or without Frenzel's spectacles, is the fact that it provides us with a curve of the eye movements which can serve as an objective basis for discussion Though the same curve may be interpreted in different ways, discussion will be more profitable if a concrete document is available rather than with a verbal description of visual impressions Furthermore, when the curves of patients are filed a good insight into the course of the disease can be obtained

Nystagmography is an important aid in ascertaining whether an eye movement is a nystagmus, a pendulum movement or an atactical movement of the eye Many strange eye movements in patients who were sent to us with the diagnosis „nystagmus" proved to be no nystagmus at the recording Atactical eye movements were seen in cerebral arteriosclerosis cerebri and in cerebellar disorders (fig 14) Tremores of the eyes due to arteriosclerosis sometimes created the impression



Fig 14 Atactical eye movements in a patient with a haemangioma cerebelli Though these eye movements looked by visual observation like a nystagmus, neither clear slow nor quick phase can be seen on the recording paper

of nystagmus (fig 15) In none of these cases a clear slow and quick phase could be discerned on the recording (JONGKEES, MAAS and PHILIPSZOON, 1962)

A peculiar finding was the fact that when we tried to provoke experimentally a pethidine nystagmus in rabbits as described by ANDERSEN, JEPSEN and KRISTIANSEN



Fig 15 Tremor of the eye lid in arteriosclerosis No slow or quick phase can be distinguished

(1953) we did not succeed in provoking nystagmus but we caused rough incoordinated eye movements (fig 16) (Bos and PHILIPSZOON, 1963)

On the other hand, patients sent sometimes with the diagnosis „wild eye movements, certainly no nystagmus", showed at the recording a clear slow and quick phase (fig 17) In these cases the velocity of the slow phase may be very high This can confuse the investigator when inspecting the eyes directly The recording solves the difficulty Galvanic nystagmus also gives strange findings on the nystagmogram (see chapter VI)

In patients with a so called „basilar insufficiancy" (HALLPIKE, 1962) we generally do not find a nystagmus but atactical eye movements instead These patients are usually over 60 years old Their audiogram shows a perception deafness, especially for the high tones

PETHIDINE

Fig. 16. Pethidine-„nystagmus"

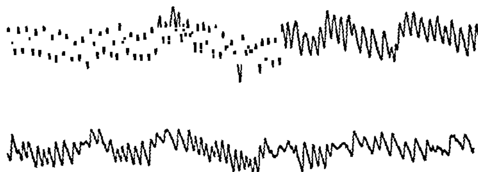


Fig. 17. Spontaneous nystagmus, which could not be determined as a nystagmus by visual observation due to the extremely high speed of the slow phase (50°—70°/sec.). On the curve a slow and a quick phase can clearly be discerned.

SUMMARY

Nystagmography is an important aid in ascertaining whether an eye movement is a nystagmus, a pendulum movement or an atactical movement

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3 *On the direction of spontaneous and positional nystagmus*

It seems important to get a better insight into the rules governing the direction of spontaneous and positional nystagmus as present in vestibular disorders of peripheral and/or central origin In literature we often find the opinion expressed that the direction of a spontaneous or positional nystagmus aids in the differential diagnosis between peripheral and central lesions

In one sided cases of Ménière's disease a spontaneous nystagmus is claimed to be beating in the direction of the healthy ear Direction changing positional nystagmus should indicate central disturbances, while in cases of pure peripheral vestibular disorders only a direction fixed positional nystagmus could be present

Recent publications (ASCHAN, BERGSTEDT and STAHLE, 1956, STAHLE 1958, JONGKEES, MAAS and PHILIPSZOON, 1962), giving the results of electronystagmographical recordings in vertigo, make it impossible to maintain these and other fixed rules about the relation between the direction of spontaneous or positional nystagmus and the site of the lesion

Performing the posture test in 13 patients with unilateral Meniere's disease, JONGKEES, MAAS and PHILIPSZOON found 4 times a direction fixed positional nystagmus to the affected ear, 6 times a direction fixed nystagmus to the healthy ear and in 3 cases a direction changing nystagmus In 41 patients, suffering from Menière's disease in both ears, they found in 14 cases a direction fixed positional nystagmus to the best ear, in 9 patients a direction fixed nystagmus to the most affected ear and 18 times a direction changing nystagmus

In 26 patients, who had a spontaneous and positional nystagmus after a radical ear operation, the above mentioned authors found a nystagmus to the operated side in 12 cases, to the healthy ear in 8 cases and 6 times a direction-changing positional nystagmus In 9 patients suffering from otitis media they found 3 times a nystagmus to the affected ear, twice a nystagmus to the healthy ear and in 4 cases a direction changing nystagmus (fig 18)

The combination of brain tumours and nystagmus is often mentioned The determination of directional preponderance in the caloric test is considered to

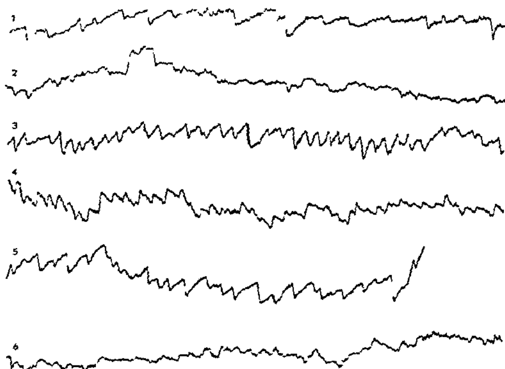


Fig 18 Direction changing positional nystagmus in a patient with one in excitable labyrinth after a radical ear-operation 1 Sitting nystagmus to the left 2 Lying on the back no nystagmus 3 Lying on the left side nystagmus to the left 4 Lying on the right side nystagmus to the right 5 Lying on the stomach nystagmus to the left 6 Head hanging position no nystagmus

give information about the site of brain tumours (CARMICHAEL, DIX and HALLPIKE, 1954, SANDBERG and ZILSTORFF-PEDERSEN, 1961)

JONGKEES, MAAS and PHILIPSZOON (1962), using electronystagmography as an indicator for caloric stimulation in 255 patients (ad modum HALLPIKE) found only 4 times directional preponderance without a spontaneous or positional nystagmus in the posture test. For this reason we used the posture test with electronystagmography, as this easy examination takes far less time than the caloric test and nevertheless enables us to find a very great percentage of directional preponderance cases Using the posture test we neither could find any rule about the direction of the nystagmus nor about the preponderance and the localisation of brain tumours

Another finding is equally strange, according to the accepted views in literature It is the fact that we recorded „gaze nystagmus" both to the right and to the left in the same patients with pure peripheral disorders When we had the patient fix his gaze — always less than 45°, to avoid nystagmus by too much deviation of the eyes — to the left, we found a nystagmus to the left and when we asked them to gaze to the right we recorded nystagmus to the right in about 40% of our patients

EXPERIMENTS

In our investigations we wanted to imitate experimentally spontaneous and positional nystagmus of peripheral and central origin in rabbits, in order to see whether we could find the rules determining the direction of that nystagmus For this purpose we studied

1 Nystagmus after unilateral labyrinthectomy
2 Nystagmus after labyrinthectomy on both sides (Bechterew nystagmus)
3 Nystagmus during alcohol intoxication
4 Nystagmus during pethidine (meperidine) intoxication
5 Nystagmus provoked by artificial brain tumours

Methods

We performed the labyrinthectomies in rabbits following the approach of De Kleyn and Versteegh Within 48 hours after the operation the rabbits were examined in the following positions in prone position on the right and on the left side in supine position and upright In order to study the Bechterew nystag mus in rabbits we performed a second labyrinthectomy on the other ear about



Fig 19 Roentgenogram of artificial brain tumour

one month after the first labyrinthectomy The movements of both eyes were recorded separately

To study the effect of alcohol and pethidine (meperidine) we examined the rabbits after administration of the drugs in the same positions as described above We administered orally 4 ml of a 96% solution of ethyl alcohol per KG body weight to the rabbits by means of a gastric tube The dosage of pethidine was 100 mg KG which we injected intraperitoneally

In order to study vestibular data in brain tumours we tried a method to imitate them by bringing a mass of foreign material into the brain substance of rabbits (PHILIPSZOON, 1963).

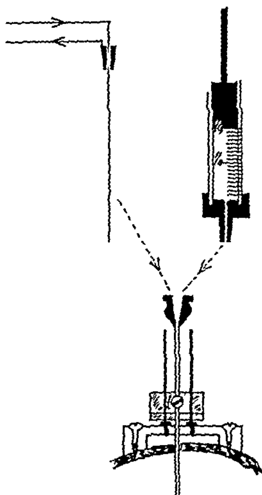


Fig. 20. Electrode with needle on stereotaxic system.

In these experiments we used the stereotaxic system of MONNIER and GANGLOFF for orientation inside the skull. To have a good chance to be in the neighbourhood of nystagmus pathways, we made our artificial tumours in the domain of the nystagmogenic centre of LACHMANN, BERGMANN and MONNIER (1958). After having found this centre for nystagmus by electric stimulation via an electrode, we injected in the same spot 0.15 to 0.25 ml of a paste of lipiodol with bariumsulphate. This paste is not absorbed and is easily localized by means of a roentgenogram (fig. 19). In order to inject the paste into the right place, we used special electrodes (fig. 20), injection needles from which the point was cut off. Through this needle the electrode was led. It consisted of an insulated piece of copper wire, whose end was free. After we had succeeded in eliciting central nystagmus by electric stimulation, the electrode was retracted from the needle. Hereafter the lipiodol barium sulphate paste was injected with a syringe. After this we examined the rabbits in the usual positions.

RESULTS

1. *Unilateral labyrinthectomy*

We operated upon 10 rabbits: 5 on the left side and 5 on the right side. Of the rabbits operated upon the left ear, one showed a direction fixed positional nystagmus to the right, while 4 had a direction-changing nystagmus. Of the rabbits operated upon on the right ear, 2 showed a direction fixed nystagmus to the left, while the 3 other animals had a direction-changing nystagmus. Thus 7 of our rabbits showed a direction-changing positional nystagmus, while 3 had a direc-

tion fixed nystagmus to the normal ear These findings do not correllate very much with the old views on the direction of nystagmus after labyrinthectomy but they confirm quite well our new clinical findings

Though these findings do not prove the existence of rules for the direction of nystagmus after labyrinthectomy, we did find, quite unexpectedly, a new „rule". In lateral position all these animals showed a much bigger nystagmus when they were lying on the operated side, while the nystagmus was very faint or absent when they were lying on the normal side In supine position the nystagmus was always smaller then in prone position (fig 21)

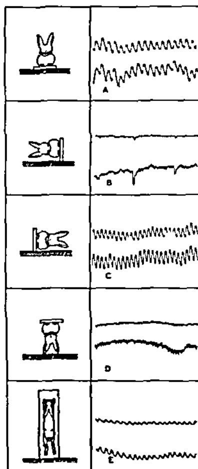


Fig 21 Positional nystagmus in a rabbit after left sided labyrinthectomy A Prone position B On the right side C On the left side D Supine position In lateral position when lying on the operated side the nystagmus is more intense than lying in the side of the healthy ear Nystagmus in prone position greater than supine position
Right eye upper curve Left eye lower curve

Another, most unexpected, finding was the fact that in the 7 rabbits with a direction-changing nystagmus, the two eyes showed nystagmus into two opposite directions when the animal was placed in one or more positions While one

eye had a nystagmus to the left, the other eye had a nystagmus to the right (fig 22). One could think that this might be due to the fact that both eyes were beating



Fig 22 Opposite nystagmus of both eyes The right eye (upper curve) is beating to the left and the left eye (lower curve) is beating to the right

in the same plane all right but that the electrodes for both eyes were not placed exactly in the same aequipotential planes, resulting in the recording of an apparently „opposite" nystagmus The fact, however, that we often found a direc-

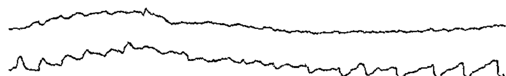


Fig 23 Direction changing nystagmus of the left eye No nystagmus of the right eye

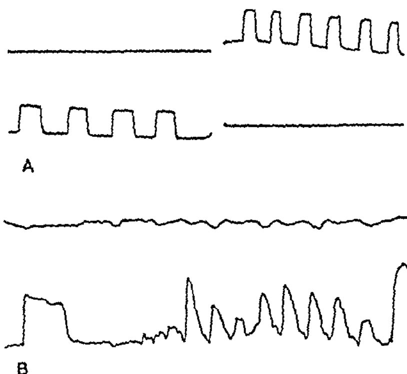


Fig 24 A Equal calibration of both channels for an input of 0,1 millivolt B Strong passive eye movements in the recording of the right eye

tion-changing nystagmus in one eye while no movements of the other eye were to be recorded (fig 23) makes this view highly improbable We often found no nystagmus in one eye, while a strong nystagmus was present in the other one

Another possible source of errors in recording the movements of both eyes is the fact that the electrical fields of the dipoles of the eyes might influence each other. To exclude this possibility we gave passive movements to one eye of normal rabbits, while recording the electric field of both eyes No influence of the moving eye could be seen upon the recording of the other eye (fig 24) (PHILIPSZOON, 1959) We always recorded the movements of both eyes with both channels on the same level of amplification, giving an identical deviation to an input step of one millivolt.

The position of the electrodes does not influence the amplitude of the recorded eye movements either. We displaced the electrodes from the brim of the eyelids in peripheral direction over more than one centimeter The recording of identical eye movements remained the same (fig 25) Identical passive eye movements were

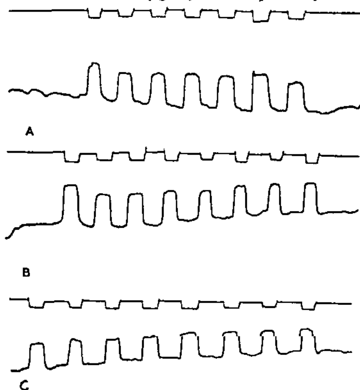


Fig 25 A Recording of identical passive eye movements B Electrodes displaced over a distance of nearly 1 cm C Electrodes displaced over 1,5 cm The upper line gives the recording of the movement of the electromagnetic relay, the lower line the eye movement Little or no influence of the displacement of the electrodes is to be observed

given by means of a thread, sutured into the cornea of the eye after local anaesthesia with pantocaine One end of the thread was led via a pulley to an electromagnetic relay while the other end was led via a pulley to a counter-weight. Switching on and off of the current in the relay thus can produce passive eye movements of equal magnitude in the rabbit's eye (PHILIPSZOON, 1959). (see chapter I)

2 *Bechterew nystagmus*

In 8 rabbits we studied Bechterew nystagmus In these animals similar results were obtained as after one sided labyrinthectomy

Two rabbits showed a direction fixed nystagmus (fig 26), while the other six rabbits had a direction-changing nystagmus In all 6 rabbits with direction changing nystagmus a nystagmus of both eyes in opposite directions was found in one or more positions of the animal

3 *Nystagmus provoked by alcohol*

We gave alcohol orally to 11 rabbits All rabbits showed a distinct nystagmus One of them had a direction fixed nystagmus and 10 showed a direction changing nystagmus (fig 27) Of those 10 rabbits, 6 had nystagmus of opposite directions in both eyes in one or more positions

Fig 26

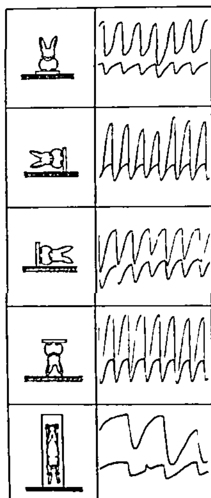


Fig 27

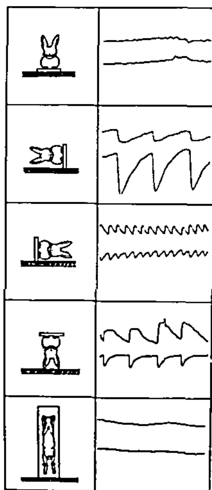


Fig 26 Bechterew nystagmus In all positions the nystagmus has about the same size
Fig 27 Alcohol nystagmus Note opposite nystagmus
Upper curve right eye Lower curve left eye

4 *Nystagmus provoked by pethidine (meperidine)*

Another form of a chemically induced nystagmus was described by ANDERSEN, JEPSEN and KRISTIANSEN (1953) Giving pethidine intravenously to patients, in order to reach some degree of anaesthesia they observed nystagmus beats before the anaesthetical influence showed itself

For this drug a certain difference of sensitivity among patients existed but as soon as the nystagmus beats appeared the anaesthetical influence became evident They did not use electronystagmography We injected similar and higher doses of pethidine intraperitoneally into 35 rabbits, but we never succeeded in recording nystagmus beats We did find very clear but incoordinated eyemovements (fig 16) which had no relation whatsoever to the well known pattern of the rhythmical movements with a slow and a quick phase which we call (vestibular) nystagmus

5 *Nystagmus provoked by artificial brain tumours*

We provoked central nystagmus by tumour formation in the centre of LACHMANN, BERGMANN and MONNIER in 12 rabbits In all these rabbits the quick phase was beating in the controlateral direction In 7 of them a clear positional nystagmus arose after injection of the artificial tumour (fig 28) In 5 rabbits no nystagmus developed In 4 rabbits the nystagmus was in the same direction as the nystagmus following electric stimulation but 3 times the nystagmus was beating in the opposite direction Thus up till now no rule could be found about the direction of positional nystagmus in this kind of artificial „brain tumours"

Further investigations are being made to get an insight into the mechanisms of the nystagmus provoked by these artificial brain tumours

SUMMARY

From recent publications on electronystagmography it appears that in patients with vestibular disorders there is often no definite relation between the direction of spontaneous or

in one or more positions a nystagmus of both eyes in opposite directions (e g in the left eye a nystagmus to the left and in the right eye one to the right!)

In lateral position after unilateral labyrinthectomy all rabbits when lying on the side of the operation showed a stronger nystagmus than when lying on the side of the normal ear (See Chapter V 4)

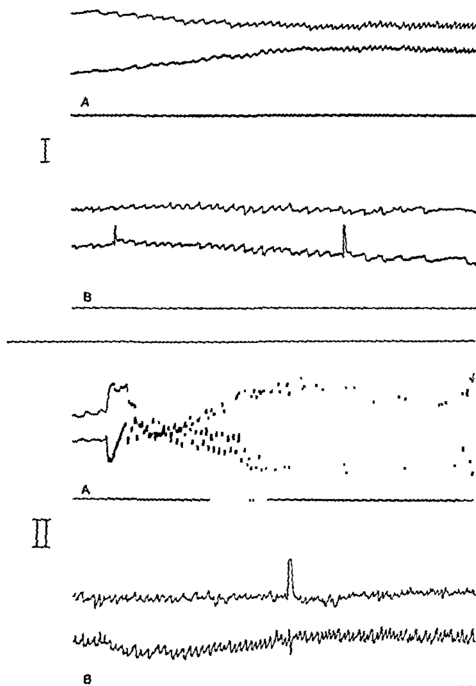


Fig. 28 Two specimens of positional
A Nysta
B Positi

A method is described to make artificial brain tumours in rabbits Paste consisting of a mixture of lipiodol and bariumsulphate is injected into the nystagmogenic centre of LACHMANN, BERGMANN and MONNIER

In 7 out of 12 rabbits this resulted in a clear positional nystagmus but without a fixed direction Further experiments are being prepared to get more insight into this phenomenon. The view that up to now no definite rules have been found about the relation between the

direction of spontaneous and positional nystagmus and the site of vestibular lesions (peripheral or central) could be confirmed by our experiments

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4 *Nystagmus and Bell's palsy*

According to the views of HILGER (1949), GODIN (1952) and others, the origin of Bell's palsy has to be sought in vascular disorder of the arteries supplying the facial nerve A spasm of the exocranial branches of the external carotid artery is thought to be the cause of Bell's palsy The vasa nutritiva (the petrosal artery and the stylomastoid artery) of the facial nerve belong to the domain of the external carotid artery Not only does the vasoconstriction provoke an ischemia of the nerve but it also gives rise to a change of the condition of the capillary walls They are damaged by anoxia Through this change, leading to a capillary hyper permeability, an abnormal transudation of the blood fluids takes place resulting in edema

The edema compresses the nerve, which causes a new obstruction of the lymphatic and venous circulation and leads to a stronger edema and in this way the vicious circle is completed

With this hypothesis in mind many decompressing operations on the facial nerve, interrupting the vicious circle, have been performed with great success In these operations an edematous swelling, mostly in the vertical part of the nerve, is indeed found Besides this swelling a mastoid is found, which contains many easily bleeding vessels, especially in the region of the facial nerve This supports the view that Bell's palsy finds its origin in a vascular disorder

Observing these bleedings in the mastoid bone we supposed it possible that

the labyrinth, especially the horizontal canal which lies very close to the facial nerve, is also involved in the process. If this should be the case, the result could be a spontaneous nystagmus and/or a diminished caloric excitability of the affected side (PHILIPSZOON, 1962).

For this reason we decided to examine an unselected group of patients with Bell's palsy. We took all the patients who visited our departement with this disorder during a certain period.

Our material consisted of 12 patients with Bell's palsy. In 11 of these cases the diagnosis was confirmed by the findings during operation. A swelling of the facial nerve, typical of Bell's palsy was found. In the one remaining case no operation was performed.

Of these 12 cases, 10 patients showed a spontaneous nystagmus in the posture test (fig. 29). 8 of them showed nystagmus in more than 2 positions. The other 2

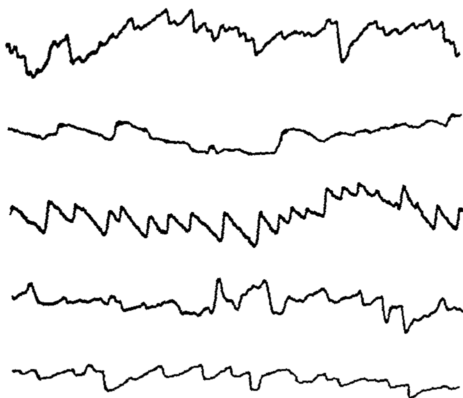


Fig. 29. Spontaneous nystagmus in some patients with Bell's palsy.

had only in one of the six positions a nystagmus, one of them with a speed of the slow phase below 6 °/sec and the other above 7 °/sec. In three cases the nystagmus was directed to the healthy ear, in six cases to the affected side and in one case a direction-changing positional nystagmus was found. These data confirm our finding that in purely peripheral labyrinthine disorders no conclusions can be drawn from the direction of the spontaneous or positional nystagmus about the site of the lesion.

The caloric test was performed in 9 of our patients. Four patients had a diffe

rence in caloric excitability, the side of the facial palsy showing a diminished reaction (fig 30) Three patients had no difference in caloric excitability, while the two remaining patients did not show nystagmus following the caloric stimulus we used

Thus six of these nine patients showed abnormal caloric reactions In our opi

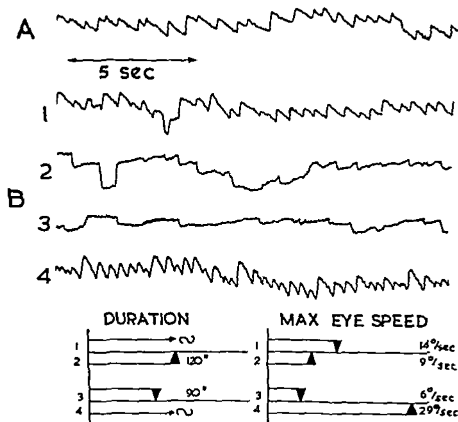


Fig 30 Patient with Bell s palsy of the left side A Spontaneous nystagmus to the right. B Caloric test showing diminished excitability of the left labyrinth 1 left cold 2 = right cold 3 = left hot 4 = right hot all 60 sec after calorization

nion one can speak of abnormal caloric reactions when with 30° and 44° C no responce is obtained as HAMERSMA (1957), STAHLE (1958) and PREBER (1959) always found a caloric response in normal subjects with the same method of caloric stimulation which we used

In our opinion the findings of this investigation support the view that the origin of Bell s palsy should be sought in vascular disorders

It is generally accepted that the cause of Meniere's disease is of vascular origin It has never been proved of vestibular neuritis or neuronitis although it has been suggested that the etiology is an inflammatory process On the other hand no peripheral vascular disorder could be excluded in vestibular neuritis (DIX and HALLPIKE, 1952, ASCHAN and STAHLE, 1956)

In our opinion, a hypothesis could be accepted that disorders of the blood vessels in the temporal bone are the primary cause of an affection which can express itself in different „diseases" such as Ménière's disease, affecting the cochlea and the labyrinth, vestibular neur„itis", affecting the vestibular labyrinth, Bell's palsy affecting the facial nerve, and in some cases of supposed Herpes Zoster oticus, in which the existence of skin lesions could not be stated with certainty.

KETTEL (1959) also mentions the investigations of MYGIND and DEDERDING (1922) who found in a series of 80 patients with Bell's palsy 12 cases of vertigo and 10 cases of acoustic lesions. Although their percentage of lesions of the internal ear accompanying Bell's palsy is much smaller than in our investigation, their findings confirm ours. Furthermore, it must be kept in mind that they didn't use electronystagmography, which makes it possible to see more vestibular disorders.

Our view is particularly supported by the case history of one of our patients. A man of 60 years experienced a facial palsy three times in his life. Twice this palsy was accompanied by vertigo, while he sometimes also complained of dizziness without a facial palsy. During the operation the aspect of the nerve proved to be typical of Bell's palsy.

SUMMARY

In a nystagmographical investigation of 12 patients with Bell's palsy a spontaneous or positional nystagmus was found 10 times during the posture test.

In 9 patients the caloric test was performed. 6 of them showed pathology.

The view is put forward that Ménière's disease, vestibular neuritis or neuronitis, Bell's palsy and some cases of supposed „Herpes Zoster" without skin lesions are all expressions of the same disease: a disorder of the blood vessels in the temporal bone affecting in various cases different organs (cochlea, labyrinth and facial nerve) exclusively or in combination with each other.

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5 *Positional nystagmus in cervical disorders*

In patients with complaints of vertigo we often find a spontaneous or positional nystagmus without any abnormality of the audiogram or the caloric test Neither are central neurological disorders to be found When we make roentgenograms of the cervical vertebral column of these patients we often find arthrosis When asked, these patients often also complain of paresthesia of the hand and pain in the neck, while dysphagia may also be present It is clear that they are suffering from the cervical syndrome which was first described by BARRÉ (1925) DE KLEYN and NIEUWENHUYSE (1927) thought that the origin of this vertigo should be sought in an obstruction of the vertebral artery disturbing the blood supply to the labyrinth

GARNETT PASSE (1951) and SEYMOUR (1954) sought the origin in irritation of the cervical sympathetic causing disturbances of the inner ear After cutting of the posterior cervical nerve roots of C_{2-5} BIEMOND (1939 and 1940) found that a positional nystagmus occurs in patients as well as in rabbits In collaboration with this investigator we were able to record positional nystagmus after cutting C_2 in rabbits (fig 31) By means of the necktorsionnystagmus (PHILIPSZOON, 1962)

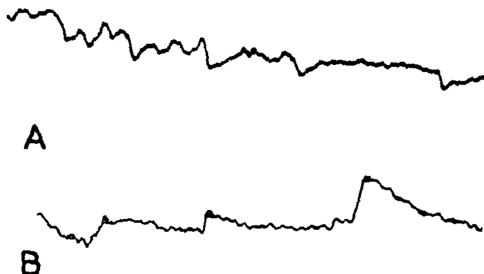


Fig 31 Positional nystagmus about 6 minutes after cutting off the second cervical root in two rabbits

we were able to lend support to BIEMOND's theory that irritation of the posterior cervical nerve roots may cause nystagmus, of non labyrinthine origin In collaboration with Bos experiments were made to deepen our insight into the mechanisms of cervical nystagmus This point will be discussed in Chapter VII

SUMMARY

We often find a spontaneous or a positional nystagmus in patients complaining of vertigo in whom no abnormalities are found of the audiogram or the caloric test. When definitely asked

about it, these patients often complain about sequels from disorders caused by the cervical syndrome, such as itching in the hands and pain in the neck. Roentgenograms often show cervical arthrosis Especially in this category of patients electronystagmography is valuable in giving objective pathologic data.

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6 *Drugs and positional nystagmus*

Reactions, provoked by angular and linear accelerations, i e , caused by stimulation of the cupulae or the maculae of the inner ear, are suppressed by the antihistaminic cinnarizine (PHILIPSZOON, 1959) (see also next chapters) In patients with vestibular vertigo its influence on the complaints could be demonstrated significantly in statistics (PHILIPSZOON, 1961, 1962)

In order to obtain more knowledge about the site of action of this drug, we investigated some forms of positional nystagmus in rabbits We standardized the method and we gave cinnarizine 40 mgm/kg body weight, to observe its influence on these various forms of nystagmus (BOS, 1962, BOS and PHILIPSZOON, 1963) We investigated the following types of nystagmus

1 Nystagmus following unilateral labyrinthectomy
2 Nystagmus after Bechterew
3 Nystagmus provoked by ethyl alcohol
4 Nystagmus provoked by pethidine

1 *Nystagmus after unilateral labyrinthectomy*

We injected cinnarizine in 8 rabbits who had undergone a unilateral labyrinth

ectomy In 7 of them an undoubtful suppression of the nystagmus was the result (fig 32)

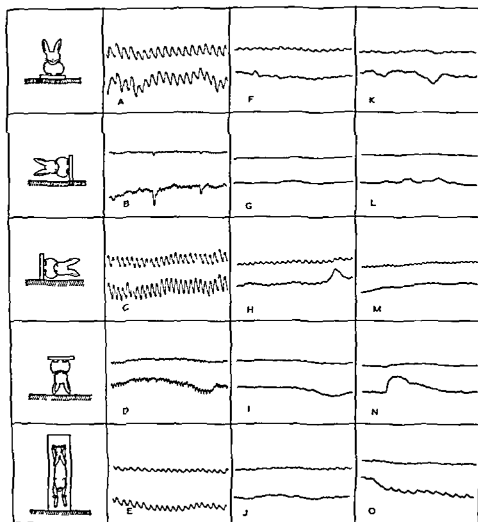


Fig 32 The effect of Cinnarizine after left sided labyrinthectomy
A — E before injection Upper tracing right eye
F — J 20 minutes after injection
K — O 40 minutes after injection Lower tracing left eye

2 *Bechterew nystagmus*

The source of this nystagmus is thought to be the spontaneous activity in the vestibular nuclei on the side of the first destroyed labyrinth This implies a truly non labyrinthine nystagmus since no peripheral activity is present anymore Studying the influence of cinnarizine 10 to 20 h after the last extirpation, we found that this form of nystagmus is also suppressed by the drug (fig 33)

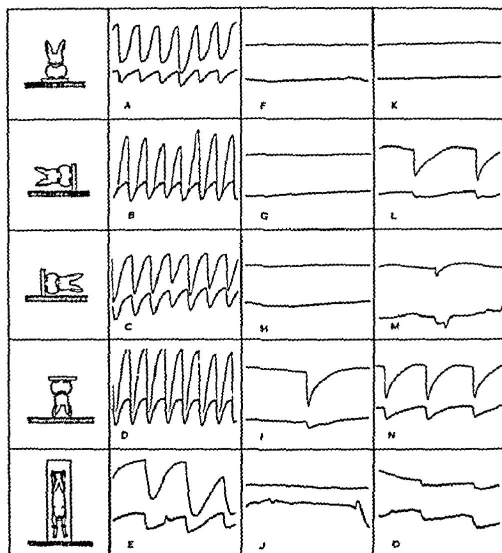


Fig. 33. The effect of Cinnarizine upon Bechterew nystagmus. Further legend see fig. 32.

This finding leads us to the conclusion that the action of cinnarizine can not be purely peripheral.

3. *Nystagmus provoked by alcohol consumption*

Ethyl alcohol 96% given to rabbits in a dose of 4 cc/kg body weight (through a stomach tube and in diluted form) provokes a typical positional nystagmus which is present after about half an hour.

It is clearly demonstrable when the animal is lying on its left side, on its right side or upside down. A dose of 3 cc/kg body weight did not constantly evoke the typical nystagmus.

ASCHAN (1957) observed volunteers intoxicated with alcohol and found a

nystagmus to the left while they were lying on their left side, and one to the right when the test person lay on his right side, whereas the directions appeared to be reversed during the hangover period

They described similar observations on laboratory animals, but they did not succeed in recording or finding an animal „hangover" Neither did we, as a matter of fact

Alcohol nystagmus cannot be evoked in rabbits without labyrinths and cinnarizine has no influence on this form of nystagmus (fig 34) So far we cannot explain why cinnarizine does not suppress this form of (peripheral?) nystagmus

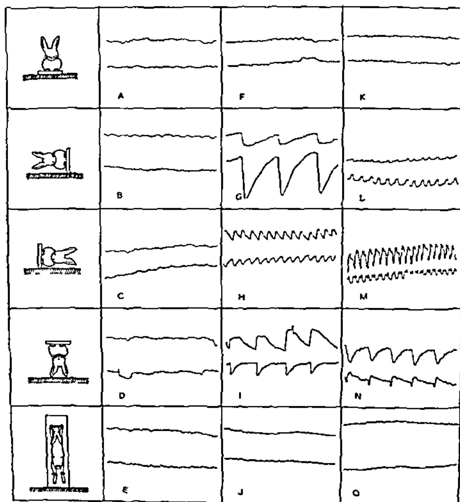


Fig 34 The effect of Cinnarizine upon alcohol nystagmus

A — E before alcohol
F — J 30 minutes after alcohol consumption
K — O 30 minutes after Cinnarizine

4 *Nystagmus provoked by pethidine*

As already discussed we were not able to provoke nystagmus by injection of pethidine into the peritoneal cavity.

We did find very clear but uncoordinated eye movements, which had no relation whatsoever to the well known pattern of the rhythmical movements which we call nystagmus (fig 16).

Cinnarizine proved to have a suppressive effect on these movements.

SUMMARY

We were able to suppress by means of Cinnarizine some forms of positional nystagmus. It suppresses nystagmus after unilateral labyrinthectomy and Bechterew nystagmus.

Cinnarizine does not suppress alcohol nystagmus in rabbits.

We did not succeed in provoking nystagmus by means of pethidine (meperidine). Rough incoordinate eye movements arose without quick or slow phase, suppressed by pethidine.

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THE CALORIC TEST.

1 *Quantitative test (modified Hallpike technique)*

Methods

Using electronystagmography HAMERSMA (1957) compared the caloric tests performed according to HALLPIKE, to KOBRAK (1922) and to VEITS (1928) in normal subjects By these investigations the HALLPIKE method proved to be superior to the other methods Therefore we chose it, be it slightly modified, for our investigations

Thus the quantitative caloric tests were performed with water of 30 and 44° C as described by THORNVAL (1917 and 1932) and by FITZGERALD and HALLPIKE (1942)

The ears were irrigated with about 250 c c of water for 30 seconds The nystagmus was recorded while the patient had his eyes closed We determined the duration and the maximum eye speed of the slow phase of the nystagmus The maximum eye speed was recorded on a derived curve according to the method of HENRIKSSON (1955, 1956) In the beginning we recorded, according to HAMERSMA (1957), simultaneously the conventional curve and the derived curve Nowadays we measure the maximum eye speed from the direct curve as this appears to be easier and to give the same results (fig 5)

As „normal material" for the caloric test we used the results of investigations in 47 healthy subjects

We thougt it important not to use the traditional absolute values for the difference in excitability of both labyrinths and for the presence of a directional preponderance As JONGKEES (1948), THOMSEN (1953), HAMERSMA (1957), STAHLE (1958) and PREBER (1958) found a great variability for the responses to the caloric test, we decided to express the difference in excitability between the two sides and the directional preponderance with a relative figure, i e in the percentage of the total excitability A difference of, e g , 40 seconds between L and R at an excitability level of 50 seconds per irrigation may be pathological, whereas the same difference of 40 seconds at a level of 300 seconds will fall completely within normal limits We gave the numbers 1, 2, 3 and 4 according to the traditional standards to the irrigations, i e , 1 = left cold (30° C), 2 = right cold (30°C), 3 = left hot (44°C), 4 = right hot (44°C) The difference in excitability between left and right was expressed in the percentage of the total excitability, as follows

$$\frac{(1+3)-(2+4)}{(1+2+3+4)} \times 100\%$$

When the right labyrinth is less excitable than the left one, we get a positive value and a negative value in the reverse case

4. *Nystagmus provoked by pethidine.*

As already discussed we were not able to provoke nystagmus by injection of pethidine into the peritoneal cavity.

We did find very clear but uncoordinated eye movements, which had no relation whatsoever to the well-known pattern of the rhythmical movements which we call nystagmus (fig 16).

Cinnarizine proved to have a suppressive effect on these movements

SUMMARY

We were able to suppress by means of Cinnarizine some forms of positional nystagmus. It suppresses nystagmus after unilateral labyrinthectomy and Bechterew nystagmus

Cinnarizine does not suppress alcohol nystagmus in rabbits

We did not succeed in provoking nystagmus by means of pethidine (meperidine) Rough incoordinate eye movements arose without quick or slow phase, suppressed by pethidine

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0 025) These findings confirm our opinion that in the caloric test relative and not absolute values should be used

RESULTS of the examination of patients with vertigo

We performed the caloric test in 255 patients complaining of vertigo These patients did not have an otitis or an ear, which had been operated upon

Directional preponderance

149 of these 255 patients did not show any spontaneous nystagmus in the position in which the caloric test was performed Only in 15 of these patients did we find a D P preponderance According to the definition we have given of pathological D P

Only in 4 patients did we find a directional preponderance without a spontaneous or positional nystagmus, whilst in 3 of these 4 patients a difference in excitability between both labyrinths was present The conclusion we have to draw from this finding, we think, is that, when electronystagmography is used and the posture test is performed, the determination of D P by coloric examination will seldom offer new aspects

Difference in excitability

In 68 patients of 255 we found a pathological difference in excitability according to our definition while both labyrinths were excitable 11 of them had only a difference as regards the duration of the nystagmus, 38 had only a difference as regards the maximum eye speed of the slow phase, while 19 patients had a difference both for duration and for the maximum (fig 35) eye speed This means that with the aid of the maximum eye speed we can find about twice as often a difference in excitability than in duration, a fact also found by STAHLE (1958) This fact also confirms the opinions of RUDING (1953), v EGMOND and TOLK (1954), HENRIKSSON (1955, 1956), ASCHAN, BERGSTEDT and STAHLE (1956), KOCH, HENRIKSSON, LUNDGREN and ANDRÉN (1960), PHILIPSZOON (1960), that the maximum eye speed of the slow phase is a more precise criterion to judge nystagmus and vestibular function than the duration of the nystagmus

Only 2 of our 255 showed a difference in excitability without a spontaneous or positional nystagmus in posture test and/or an abnormal audiogram 9 showed a difference in caloric excitability, while they had an abnormal audiogram without a spontaneous or positional nystagmus, 5 had a difference in excitability with a nystagmus in the posture test and a normal audiogram

Thus in only few cases the caloric test will give new information after the posture test and the audiogram have been performed

When perception deafness is found with recruitment in the presence of nystagmus in the posture test no caloric test is necessary to strenghten the diagnosis of Meniere's disease,

The directional preponderance (D. P.) was also expressed as a percentage, as already proposed by JONGKEES in 1948. The difference between the right and the left beating nystagmus was expressed in the percentage of the total excitability:

$$\frac{(1 + 4) - (2 + 3)}{(1 + 2 + 3 + 4)} \times 100\%$$

Consequently we find in case of a D. P. to the right a positive value and a negative value in case of a D. P. to the left.

Of our 47 normal subjects we calculated the mean and standard deviation for the difference between L and R and for the D. P. both for the duration and for the maximum eye speed.

As regards the duration we found as the mean for the difference between L and R $-$ 0.8%, *with a standard deviation of 6.7%*.

For the maximum eye speed of the slow phase we found as the mean for the difference between L and R + 0,8%, with a standard deviation of 7.5%. For the directional preponderance we found as regards the duration a mean of $-$ 4% with a standard deviation of 15%, whereas we found for the maximum eye speed of the slow phase a mean of $-$ 1.1% with a standard deviation of 8.7%.

On the strength of these findings we called a difference in excitability or a directional preponderance abnormal in our patients when the values differed more than the double standard deviation from the mean. We called a difference between L and R pathological as regards the duration when it exceeded the values $-$ 14% or + 14% and as regards the maximum eye speed $-$ 15% or + 15%. We called a D. P. pathological as regards the duration when we found its value exceeding $-$ 30% or + 30% and as regards the maximum eye speed if its value exceeded $-$ 18% and + 18%. The values as regards the duration for the D. P. are still higher than those of JONGKEES in 1948, who proposed 20% of the slightest excitable nystagmus, i.e. less than 10% of the total excitability.

To find out whether our hypothesis was correct, we tested the combined normal material of HAMERSMA and PRUBER with the test of WILCOXON. We divided their patients into three equal groups. In the first group we placed the subjects with weakly excitable labyrinths, in the second group the subjects with a medium excitability of the labyrinths and in the third group the subjects with the most highly excitable labyrinths.

We found that, as regards the duration, *both for the difference in excitability* and *for directional preponderance*, the values found in group III were significantly higher than those in group II (P< 0.025) and those in group II higher than those in group I (P < 0.025).

As regards the maximum eye speed we did not find significant differences between the values of group I, II and III. The probability found for those values was about 10%. This is higher than the conventional level for significance. But when we devide the material into two equal groups, group A, that with the least excitable labyrinths and group B, that with the most excitable labyrinths, we found a significant difference between the values of group A and group B (P <

In his thesis VAN NIEUWENHUIJSEN (1958) describes how after a storm was over, the passengers on board ship still showed symptoms of seasickness for a considerable time

Afterwards KLIJN AND EK (1959) showed that similar symptoms may also arise in pigeons They stimulated pigeons with a sinusoidal rotatory movement As a result of acceleration reflectory eyemovements arise which have the same sinusoidal pattern as the stimulus About four hours after a pigeon was no longer subject to the stimulus mentioned above the original sinusoidal pattern could still be found in the spontaneous head movements The head movement they found was perfectly identical to the response obtained under stimulation

We found a similar phenomenon For the determination of the slow speed of the nystagmus, we often used the method of HENRIKSSON (1955, 1956) In order to calibrate the eye movements for this examination we make the patients perform a sinusoidal eye movement by asking them to follow the movement of a pendulum with their eyes After the calibration, during which he is seated in a chair the patient is laid on a stretcher, in a reclining position with closed eyes, for the performance of the caloric test

In one patient we still saw eye movements on the nystagmograph paper after the patient had been placed on the stretcher and had been requested to close his eye The movements were perfectly identical to the ones the patient had been forced to make during the calibration test This must have been the result of an inculcation of this eye movement in the mind, a central „memory" function (fig 36) (PHILIPSZOON, 1960)

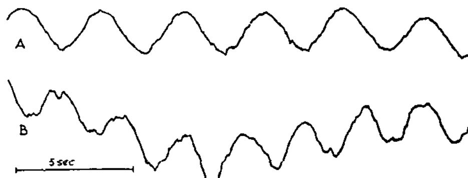


Fig 36 A Calibration The patient is visually following the swinging of a pendulum B Spontaneous eye movements of the patient who is lying on a stetcher with closed eyes, about five minutes ater the calibration

In contrast to the observations of KLIJN and EK in a pigeon, there was no question of a recollection of a movement as a result of a vestibular stimulus, but of „memory" reproducing the recollection of an eye movement made at will

Later with our attention focussed to it we observed the same phenomenon in many other patients Although often pendulum movements of the eyes can be recorded in patients especially when they are dozing (ASCHAN, BERGSTEDT and STAHLE, 1956, HAMERSMA, 1957, LANGE and KORNHUBER, 1962) we are still

often struck by the sinusoidal regularity of these movements in some patients, directly after they have been subjected to calibration. Further extensive experiments are being prepared to deepen our insight into this phenomenon and to test our hypothesis.

From our observations we think some conclusions may be drawn in respect to the duration of the nystagmus in the caloric and rotation tests.

If it is true that a recollection of eye movements exists expressing itself in the continuation of them after termination of the stimulus, we may assume that this memory function can also affect the duration of the nystagmus in labyrinthine tests.

For, when the cupula is no longer stimulated, there can still be a nystagmus, which is the result of this assumed memory function. In that case the eye movements are the nystagmus beats caused a short time before by vestibular stimulation and afterwards „remembered", and not the result of a direct vestibular stimulation.

Possibly this also accounts for the fact in the caloric test the maximum speed of the slow nystagmus phase has proved to be a more sensitive, and especially a more reliable criterion of the excitability of the labyrinth than the duration of the nystagmus (VAN EGMOND and TOLK, 1954, HENRIKSSON, 1955 and 1956, ASCHAN, BERGSTEDT and STAHLE, 1956, HAMERSMA, 1957). The fact that the reaction of the labyrinth in the caloric test is rather an indication of the temperature wave through the mastoid bone, is also a cause for faults in the measurement of the duration of labyrinthine excitability (JONGKEES, 1950). Also, in the rotation test with its more physiological way of stimulating the semicircular canals, we find indications that the duration of the post rotatory nystagmus is not quite correlated with the maximum speed of the slow nystagmus phase as HENRIKSSON (1955) found in cupulometry. This indicates that the phenomenon of memory might also affect the duration of the nystagmus in the rotation test.

The after reactions after optokinetic nystagmus found by ASCHAN, BERGSTEDT and STAHLE (1956), HAMERSMA (1957) and MCLAY, MADIGAN and ORMEROD (1958, 1959), are possibly of the same character. Though the secondary phase nystagmus *after optokinetic nystagmus of some duration is generally in opposite* direction it is surely of central origin.

SUMMARY

The sinusoidal curves of the eyes used for the calibration of nystagmograms are sometimes found after many minutes in the spontaneous movements of the eyes behind closed eyelids. This "memory" may be of influence upon the duration of reactive nystagmus (caloric, rotation tests).

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3 *Qualitative caloric test with Ethyl chloride*

We are often confronted with the great problem of performing caloric tests in patients with a dry eardrum perforation A great problem indeed, for in case an ear with a dry perforation is irrigated with cold or hot water re infection is highly probable

To avoid this chance of re infection and still to be able to perform a caloric test on the labyrinth, we can elicit caloric reactions by means of a piece of cotton wool soaked in ethyl chloride As ethyl chloride evaporates immediately, the chances of making a dry ear wet again are exceedingly small

We investigated this old method with the aid of electronystagmography (PHILIPSZOON, 1960)

In order to state that a labyrinth has a normal caloric reaction it must be possible to provoke a nystagmus both to the right and to the left This is usually done by irrigating the ear with cold and hot water To see whether a nystagmus could be elicited with ethyl chloride, we stimulated the patient's labyrinth by laying a small piece of cotton wool soaked in ethyl chloride, against the posterior wall of the external ear meatus over (the rest of) the eardrum To examine a patient with ethyl chloride we performed the investigation while he was lying both on his back and later on his abdomen In this way we could provoke a nystagmus both to the right and to the left from each ear

We investigated the possibility of eliciting caloric reactions with ethyl chloride in ten persons who had normal reactions with cold and hot water (30 and 44 centrigrade) We tried, in vain, to perform quantitative caloric reactions with ethyl chloride Neither was it possible to state whether there was a directional preponderance or not But if a nystagmus could be caused with water, it could also be elicited with ethyl chloride

We found that all ten subjects reacted with nystagmus when we applied a small

piece of cotton wool soaked with ethyl chloride during 30 to 60 seconds against the posterior wall of the external meatus right over the drum (fig. 37).

In this way we also investigated the caloric reactions in more than fifty patients with dry eardrum perforations. We did not find the slightest sign of re-infection or irritation.

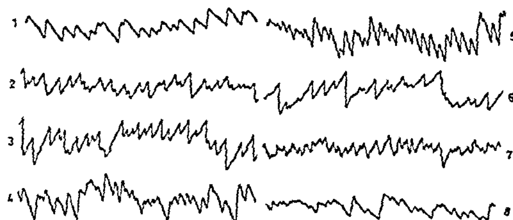


Fig. 37. Caloric reactions of the same subject with water and ethyl chloride. An upward movement indicates an eye movement to the right and v. v.

1. Left ear, cold water
2. Right ear, cold water
3. Left ear, hot water
4. Right ear, hot water
5. Left ear ...
6. Righ...
7. Left ...
8. Righ...

SUMMARY

It ...
with ...
quin ...

REFERENCE

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CHAPTER IV

THE ROTATION TEST

1 *Cupulometry*

Post rotatory reactions, particularly nystagmus, have been investigated in patients since BARANY (1907) introduced his rotation test.

When a person is placed in a rotation chair, and he is turned round with constant velocity, the deviation of the cupula provoked at the beginning of the rotation by the initial acceleration, will disappear completely. A state of equilibrium is reached, in which the subject has no turning sensations, neither are there any reflexes. When the movement is stopped, a deviation of the cupula arises, this time in the opposite direction and caused by the deceleration. The sensations and reactions both have a direction opposite to that during the acceleration phase. In the BARANY test the subject was turned ten times in twenty seconds, and then the movement was stopped abruptly. In this way the longest possible post rotatory nystagmus was supposed to arise. Many objections may be raised against this method, which was used very much and which is still used. The most important objection is, indeed, that in this way no well-dosed stimulus can be given. The cupula, which deviates under the influence of the great initial acceleration, does not by any means return to its original position during the period of constant velocity which lasts less than twenty seconds. The abrupt stopping of the turning chair stimulates the cupula while it is still in a deviated position. It is clear that it is impossible to give an accurately dosed stimulus to the cupula in this way.

The method of VEITS (1931) may be considered a great improvement. The subject is set in motion so gradually that the cupulae are not stimulated as the stimulus remains subliminal. This very slow acceleration is maintained until a speed of 180°/sec. is reached. At this velocity the subject is rotated for a few minutes until the cupula is surely at its zero position. This may be concluded from the absence of nystagmus or sensations. Only then the turning is stopped. We can now be reasonably sure about the size of the stimulus for the cupula. The stimulus, however, is too strong to be called physiological. Quite to the contrary the probability that the subject will experience nausea is rather high and there is a real danger that a sick labyrinth will be damaged (VAN EGMOND and JONGKEES 1948).

Cupulometry (VAN EGMOND, GROEN and JONGKEES, 1948) is a rotation test in which small, harmless stimuli — physiological as regards their size — are given. In cupulometry we measure the duration of the post rotatory nystagmus and of the after sensation. The subject is sitting in a rotating chair with the head bent forward 30°. The horizontal semicircular canals are then situated in the plane of rotation. Under these circumstances only the horizontal canals are stimulated. The subject is gradually set in rotation, until a constant velocity has been reached. After a short period the endolymph in the semicircular canal does no longer flow. This can be checked by the absence of nystagmus beats on the registration

paper of the nystagmograph. The chair is then stopped within about one second. In this way it is possible to administer well dosed stimuli to the cupula at different rotatory velocities. When we graph the duration of the post-rotatory nystagmus or the duration of the after-sensations in seconds as ordinate against the magnitude of the stopping impulse from a certain angular speed in degrees per square second as abscissa, the latter arranged on a logarithmic scale, we obtain a straight line. Such a graph is called a cupulogram.

Although this method has proved to be of outstanding value, it is laborious and takes much time. Nowadays we prefer as routine clinical rotation test the *torsion swing test*, which is much easier and takes far less time. Cupulometry being an accurate method particularly when using electronystagmography we studied the effect of drugs upon the cupula with this technique (see further in this chapter).

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2. *The torsion swing. A simple rotation test*

Although electronystagmography is a valuable aid in clinical work it cannot replace the measurement of the post-rotatory sensation as done by means of cupulometry (VAN EGMOND, GROEN and JONGKEES). For the determination of the post-rotatory nystagmus, however, it proved to be very valuable (STAHLE, 1958). The determination of a directional preponderance by means of cupulometry, has however, little advantage over the posture test, a procedure much easier to find a D.P. (see chapter II).

The reason why we still present another method is that by means of electronystagmography it is very easy to record perrotatory nystagmus. We developed a very easy and quick test, which enables us to determine a D.P. in rotatory tests within a few minutes (DE BOER, CARELS and PHILIPSZOON, 1963).

Using the torsion swing (MACH, 1875, VAN EGMOND, GROEN and JONGKEES, 1949) we can stimulate the horizontal semicircular canals with angular accelerations. When we let the swing move freely, damped sinusoidal movements are obtained. Experiments with sinusoidal stimulation in the rotation test were also described by HENNEBERT (1956) and GREINER (1962).

The torsion swing is a very simple and cheap instrument. It consists of a seat, which is hung by means of two cables from the ceiling. The seat of the swing is coupled by means of a flexible shaft to a linear potentiometer on the floor. The potentiometer is part of a bridge of Wheatstone. This makes it possible to record

the movements of the swing The swing can be rotated in the horizontal plane to stimulate the two horizontal canals (fig 38) The electrodes for electronystagmography are placed on the two temples in order to record horizontal eye movements A ground electrode is placed on the forehead

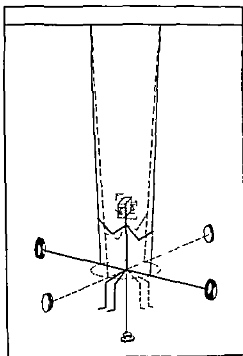


Fig 38 Scheme of torsion-swing

Before we let the swing move freely we keep it at a position of 90 degrees from its zero point We always cause the first swinging to be anti-clockwise and the second clockwise In this way the beats of the nystagmus are directed towards the left during the anti clockwise acceleration and towards the right as its direction changes and so further alternately to the left and to the right (fig 39) We now count the number of nystagmus beats to the left and to the right during the first ten swingings (fig 39) The difference between the total number of beats to the left and to the right is then expressed in a percentage of the total number of nystagmus beats in the following way

$$\frac{(L - R)}{(L + R)} \times 100\%$$

The necessity to express a D P in a relative and not in an absolute number has been discussed above

Besides nystagmus compensatory eye movements can be recorded on the torsion swing as well When the excursions of the swing are very small, we can observe varying eye-deviations, which are essentially the expression of the slow

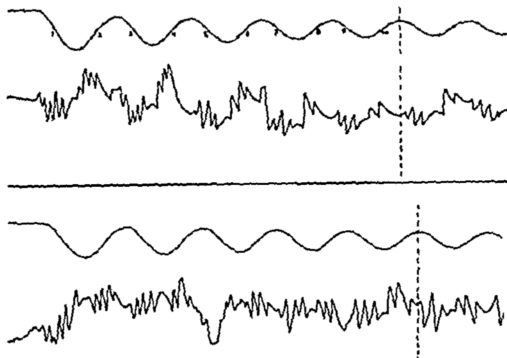


Fig. 39 . . . op
Upper line movement . . .

nystagmus phase (fig. 40). When the stimulus of the swing is small, the slow phase does not reach the critical value to provoke a quick phase (PHILIPSZOON, 1962). This phenomenon was observed both in rabbits and in human beings. At the beginning of the swing movements, when nystagmus is present, we can clearly observe compensatory eye movements as well (fig. 39 and 40). We can see that

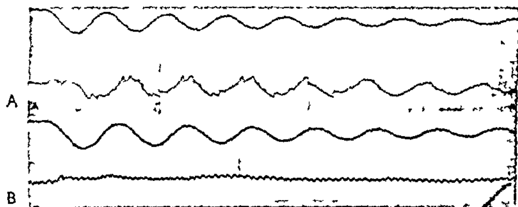


Fig. 40. Recording of eye movements of the rabbit on the torsion swing. The upper line indicates the movements of the swing, the lower line represents the recording of the eye movements. A. Normal rabbit: first nystagmus to both sides is seen, which passes into compensatory . . vements. B. Labyrinthless rabbit: no reaction is observed.

ements

This leads to the hypo . . . isms one of the slow and one of the quick phase. They both have . . . terns

tics and threshold values Thus, the usual determination of the threshold of complete nystagmus will not be the threshold for the labyrinth but the threshold of the quick phase, i e, a compensatory mechanism which is localised centrally and overrides the slow phase If the quick phase does not show on the torsion swing, a basic slow phase remains, varying in direction These remaining varying deviations on the torsion swing are essentially and literally as much compensatory eye movements as the mostly so-called corrective influences which are caused by the otoliths The findings of EK, JONGKEES and KLIJN (1959) also point in

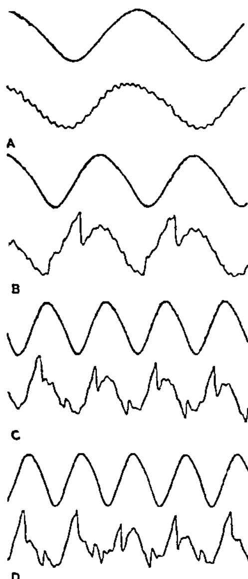


Fig. 41 Recording of eye movements provoked by sinusoidal angular accelerations The compensatory eye movements (A) pass into nystagmus (B-D), when the frequency of the sinus is heightened
Upper line movements of the swing Lower line eye movements

that direction. Namely, they found a much lower threshold for the head nystagmus in pigeons than had been assumed before, but they determined the slow phase limen during sinusoidal stimulation. In the experiments on the torsion swing (a damped sinus movement) we could prove, both in rabbits and in human subjects, an evident transition from nystagmus to varying eye deviations and vice versa. Further experiments were made with a common undamped sinusoidal movement, which also showed that a low stimulus provoked varying eye deviations only, which passed into nystagmus as the stimulus increased. This could be achieved both by enlarging the amplitude or the frequency (fig. 41).

Here again we see, that electronystagmography can show more details than could ever be observed by the unaided eye. The latter method, only shows the threshold of the quick phase of the nystagmus.

For the standardization of our method we examined 80 normal subjects on the torsion swing. We calculated the mean and the standard deviation of the distribution. This was done for the difference between left beating and right beating nystagmus. As the mean we found + 1,2%. The reason that this is not zero and that this figure has a positive sign, can be explained by the fact that our first swinging was always to the left, which makes the total stimulation provoking nystagmus to the left greater than the stimulus for nystagmus to the right. As standard deviation we found 11%. Hence we propose to call a value for the difference between left and right beating nystagmus lying beyond + 23% and − 23% (double standard deviation) a pathological directional preponderance, since less than 5% of normal subjects have a directional preponderance of this size.

SUMMARY

A simple rotation test, the torsion swing test, is used as a clinical method of examination of the horizontal canals. It takes only some minutes to perform this test.

The perrotatory horizontal nystagmus during movements of this swing is recorded. The difference between the total amount of nystagmus beats to the left and the total amount of beats to the right during the first ten swingings is expressed as a percentage of the total number of beats. The mean and standard deviation of this difference between left and right beating nystagmus in 80 normal subjects were calculated. A directional preponderance bigger than 23% (double standard deviation) is taken as an indication of pathology.

Nystagmus consists of two components: a slow eye deviation and a quick corrective phase. The threshold of the first is much lower than that of the second. The quick corrective phase only occurs when the slow eye deviation has reached a critical value.

It is possible, with a small angular acceleration, to provoke compensatory eye movements only, which, when the stimulus is increased, pass into nystagmus. This was demonstrated with a damped sinus movement which was elicited by means of the torsion swing.

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3. *The effect of some drugs upon reflexes provoked by angular accelerations*

By means of electronystagmography we were able to develop easy methods for the investigation of the effect of drugs upon labyrinthine reflexes (PHILIPSZOON, 1959, JONGKEES and PHILIPSZOON, 1960)

For the rotation test in rabbits we used a platform, which was rotated over an angle of thirty degrees by means of a counter weight (fig 42)

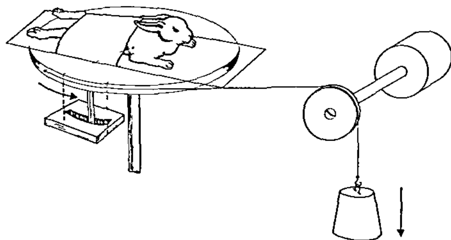
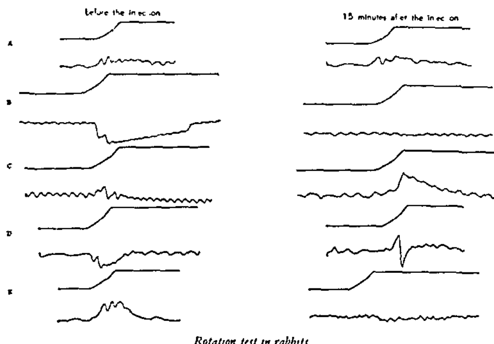


Fig 42 Scheme of the rotation table for rabbits

We examined the influence of Cinnarizine*, Chlorpromazine (Largactil), Hyoscine (Scopolamine) and Nembutal upon this nystagmus (fig 43)

Cinnarizine clearly suppressed the post rotatory nystagmus Pharmacological

* Cinnipirine Mitronal, Glanil, Stutgin, Midronal, Marison = N benzhydryl N' transcinnamylpiperazine, an anti histaminic drug of the N V Amsterdamsche Chininefabriek in Amsterdam



Rotation test in rabbits

Fig. 43. The upper line represents the movement of the table. The lower line represents the eye movement.

A. normal saline solution 10 ml; B. Cinnarazine 40 mg/kg; C. Largactil 8 mg/kg; D. Hyoscine 500 mg/kg; E. Nembutal 20 mg/kg.

and clinical studies on cinnarizine have been published by VAN PROOSDIJ-HARTZEMA and DE JONGH (1959), by WAHNER and PETERS (1960).

Chlorpromazine only suppressed the quick phase of the nystagmus. The slow phases accumulated, so that a deviation of the eye to one side was apparent on the nystagmogram. The eye did not return to its original position. On the paper the curve returns slowly to the zero line. This is an artefact due to a property of our amplifying system. (A.C.)

Hyoscine did not suppress the nystagmus. On the contrary, with the higher dosages there was some indication that the amplitude of the nystagmus increased. Our findings suggest that the effect which hyoscine is reported to cause in seasickness, cannot be due to a suppression of the vestbular excitability.

Nembutal suppressed the nystagmus only when the rabbit was completely anaesthetized.

The suppressing effect of antihistaminic drugs upon the labyrinthine reflexes cannot be due to general sedative action. In our experiments with cinnarizine the rabbit behaved normally though the nystagmus was clearly suppressed. Furthermore ARNER, DIAMANT and GOLDBERG (1954) and ASCHAN, BERGSTEDT and GOLDBERG (1957) found that amphetamine did neither change the effect of antihistamines against motion sickness nor the suppression by antihistamines of the nystagmus provoked with alcohol. On the other hand they observed that amphetamine counteracted the drowsiness caused by the antihistamines.

It is conceivable that a drug influences nystagmogram curves, not by changing the movements of the eye but simply by altering the electric charge of the eye If for instance a drug reduces the Corneo-retinal potential difference (C R P) to zero, a straight line is to be expected, whether the eye moves or not When this is taken into consideration it is clear, that we must exclude the possibility of an action of the drug via an effect on the C R P and not on the movement of the eye, in every case where a drug modifies the nystagmogram

To exclude this possibility we investigated the action of the above mentioned drugs upon the C R P For this we used the method for measurement of the C R P described in chapter I None of these drugs affected the C R P (fig 10)

In order to find more evidence on the site of action of Cinnarizine (central or peripheral) we also investigated the influence of this drug upon electrical activity derived from the nystagmogenic centre of LACHMANN BERGMANN and MONNIER (1957 and 1958) during rotation After having found the nystagmogenic centre of the above mentioned authors we succeeded in recording central electric activity from it during rotation Cinnarizine simultaneously suppressed the nystagmus and the central activity (fig 45)

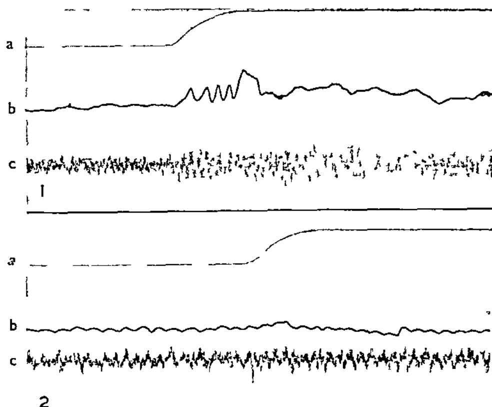


Fig 45 Suppressing effect of Cinnarizine upon nystagmus and central activity

1 before administration of drug 2 after administration of drug a movement of rotating table b eye movements c electrical activity

Encouraged by the results of cinnarizine in rabbits we also investigated this drug in human subjects. For this purpose we used cupulometry recording the nystagmus (fig. 46). In a double blind trial we clearly found a significant effect of Cinnarizine both on post-rotatory nystagmus and sensation.

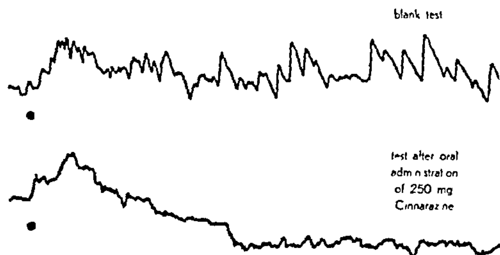


Fig. 46. Postrotatory nystagmus after stopping at a speed of 60 degrees per second. The point indicates the moment of stopping. Blank test. Test after oral administration of 250 mg. of cinnarizine.

SUMMARY

The effect of some drugs upon reflexes provoked by angular accelerations is investigated.

Cinnarizine has a suppressive effect upon rotatory nystagmus in rabbits and human subjects. This drug also suppresses the post rotatory sensation.

Chlorpromazine only affects the quick phase of the nystagmus. Hyoscine gives an increase of rotatory nystagmus.

Nembutal suppresses nystagmus only when a total narcosis of the rabbit is obtained.

Cinnarizine suppresses central electrical activity derived from the centre of LACHMANN, BERGMANN, and MONNIER during rotation.

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THE PAR

1 *Introduction and description o*

The natural stimulus for the o on.
Some authors (MAGNUS and DE NO, 1931, TER BRAAK, 1936) hold that both an can be perceived by the semicircular canals
JONGKEES and GROEN (1946) two stimuli (angular and linear accelerations) to be pe organ or organs They found that the indication time (i a stimulus to provoke the maximum reaction in an orga. mulated organ requires to quiet down again (to be ascer axes and the after sensation) is roughly three hundrec angular than for a linear acceleration. PHILIPSZOON (1962 for this theory (see further in this chapter)
On the strength of the above men we assume that angular accelerations are perceived by mean and linear accelerations by the otoliths
We were now confronted with the pr could subject rabbits and human beings in a simple way to linear accelerations and how we could best study reflexes caused by such a stimulus
SJOBERG wrote in 1931 „It is extremely probable that small reflex eye movements, invisible to the naked eye, occur in the case of rectilinearly accelerated vertical movements"
NELISSEN (1934) and RUYS (1945) described eye movements caused by linear accelerations in rabbits and guinea pigs
JONGKEES and GROEN (1946) described compensatory eye movements in rabbits that were swung on a parallelswing They observed these eye movements with the unaided eye The parallelswing also enabled them to study sensations accompanying changes in position caused by linear accelerations.

Parallel swing tests in rabbits

For our investigations the parallel swing appeared a suitable instrument Our aim was to develop a method which would enable us to record the eye movements with the aid of the nystagmograph
The parallel swing is a very simple instrument, a stretcher or another bearing surface, which is hung on four cables of equal lenght fastened to its angles. The parallel swing can be swung in two directions, the bearing surface remains horizontal during the swinging, because the junctures of the cables to the ceiling are perpendicular above the junctures to the bearing surface The mass of

swinging is shown by fig. 47. If one uses this set up, two kinds of linear accelerations, one in the horizontal plane and the other in the vertical plane arise, both with a sinusoidal pattern. The vertical linear acceleration may be neglected because according to estimations of JONGKEES and GROEN (1946) it remains far below the minimum perceptible if the size of the swing and its cables are favorable. *In the mid position of the swing the horizontal acceleration is zero and* the speed maximal. In the extreme positions the speed is zero and the acceleration or deceleration maximal. Velocity and acceleration differ 90 degrees in phase. As no angular acceleration arises the cupulae are not stimulated. For rabbits we

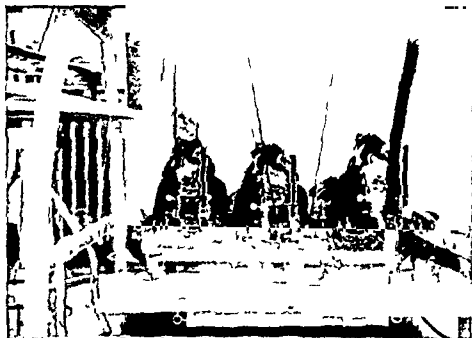


Fig. 47. Rabbit in normal position on parallelswing. Three superimposed photographs indicating the movement of the swing.

made a parallel swing that could be deviated sideways by means of a thread. The rabbit was swung sideways. The swing moved in 2,2 seconds to and fro. The initial amplitude was 22 cm, the lenght of the cables was 112 cm, the maximum acceleration was 192 cm/sec,[2] the maximum speed 65.3 cm/sec.

Swinging it along its longitudinal axis causes rotatory movements which do not change the electric field around the eye and cannot be recorded.

When we moved the rabbit sideways we did succeed in recording (fig. 48) compensatory eye movements (PHILIPSZOON, 1959).

From the above mentioned experiments it followed that the axis of compensatory eye movements is perpendicular to the direction of the movement and perpendicular to the direction of the force of gravitation.

The rabbit was bound on a board, its head being fixed in a clamp, and the experiments were carried out in the dark. The mechanical movement was recor

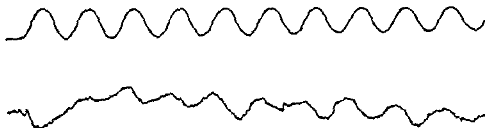


Fig 48 Recording of eye movements of a rabbit in normal position The upper line indicates the movements of the swing, the lower line the eye movements of the rabbit

ded, being translated into electrical terms by means of a potentiometer The axle of the potentiometer was placed end to end with the turning point of one of the four cables and connected with the cable In this way the movement of the parallel swing could be recorded exactly, enabling us to check the initial amplitude to the swing

Parallel swing tests in human subjects

In the same way as described for rabbits we also can record in human subjects eye movements provoked by the linear accelerations on the parallelswing

We found that a parallel swing constructed from a normal sized stretcher hung on steel cables, was not sufficiently stable When it was swung, torsion movements easily arose, as a result of which the movement of the swing became distorted These disturbing movements provoked stimulation of the cupulae, causing frequent nystagmus beats This complicated the interpretation of our results very much

In our endeavours to construct a more stable parallelswing we had two alter[illegible] In the first place we could hang the parallel swing on steel bars instead of [illegible] into one particular direction [illegible] uch would give less chance of torsion [illegible] much cheaper than that of [illegible] ly be the only possible solution

Our bearing surface had a square frame of steel tubes, 2 metres wide In the middle of the frame two other tubes were welded, between which canvas was fixed, having the size of a normal stretcher (fig 49)

The initial amplitude of the swing was always 58 cm The lenght of the cables was 338 cm The maximum acceleration was 167 cm/sec^2 The maximum velocity was 98 6 cm/sec

The torsion movements of this swing were very slight indeed In recording compensatory eye movements no nystagmus was observed, hence this parallel swing satisfied our requirements Just as with the parallel swing for rabbits the movements of this swing were also registered with a linear potentiometer

In human beings as well as in rabbits compensatory eye movements consist of a rotation about an axis of the eye, perpendicular to the direction of the force

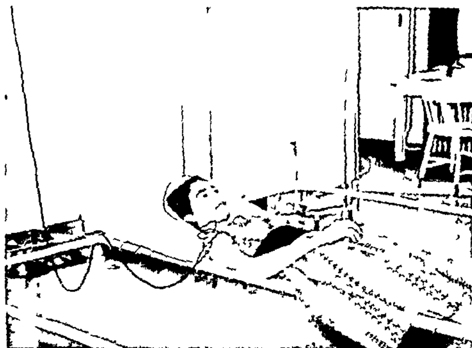


Fig. 49. Human subject on parallel swing.

of gravitation. We found that compensatory eye movements (fig. 50) cou be recorded when the subjects were lying or sitting when they were swung forward/backward direction. In subjects swung in this way, the electrodes h

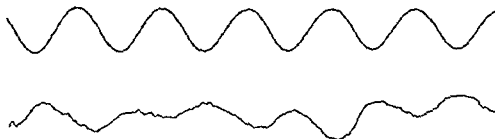


Fig. 50. Compensatory eye movements in a human subject on the parallel swing. Upper line: movements of the swing. Lower line: eye movements.

to be fixed above and below the eye. When the swing was moved sideways, e movements could only be registered when the subject was lying on his bac It was not possible to record eye movements when the subject was sitting ai swung sideways because then the axis of rotation coincided with the electric axis of the eye.

For our experiments we preferred to swing the subject sideways in lying atti tude. The electrodes were fixed in the same way as in the rotation test in tl temporal region. This was far easier than fixing the electrodes above and belo the eye. In our experiments we gave the subject always the same initial amplituc

by starting from the same deviated position This could be checked as in the test in rabbits with a linear potentiometer

The head of the subject was fixed in order to eliminate as much as possible disturbing movements of the head relative to the underlayer

In the parallel swing tests in human subjects we could calculate the amplitude of the eye movements that occurred during the swinging and we could express the eye rotation in degrees

Calibration took place in the usual way This movement was recorded with the nystagmograph The eye movements which occured when the subject was swung on the parallel swing could now be expressed in degrees eye rotation The total eye rotation during the first ten swingings can be measured

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2 *The proper stimuli for the otoliths*

JONGKEES (1944) and JONGKEES and GROEN (1946) were the first since MACH (1875) and BREUER (1874 and 1891) to draw the attention to the fact that in vestibular stimulation there is no fundamental difference between linear accelerations represented in dynamic, static and centrifugal forces

MAGNUS and DE KLEIJN and with them a whole generation of labyrinthologists had accepted such a differentiation for so-called static and dynamic stimuli

JONGKEES and GROEN divided the labyrinthine reflexes as follows

1 Reflexes and sensations caused by angular accelerations
2 Reflexes and sensations caused by linear accelerations

They made it highly probable that the angular and the linear accelerations are the proper stimuli for the semicircular canals and the otolith-organs respectively

Electronystagmography has made it possible to study vestibular eye reflexes

more accurately than before We therefore used this method for experiments concerning the function of otoliths and semicircular canals

After having developed a method to record electronystagmographically eye movements caused by the linear accelerations of the parallel swing (PHILIPSZOON 1959, JONGKEES and PHILIPSZOON, 1960 and 1962) we used this method to study JONGKEES' and GROEN's hypothesis (PHILIPSZOON, 1962)

Methods

To provoke linear accelerations we used the parallel swing To provoke angular accelerations we used the torsion swing (chapter IV)

In order to perform total and partial labyrinthectomies, we operated upon rabbits after the technique of VERSTEEGH (1927)

In rabbits with partial labyrinthectomy on one side the other ear was always totally labyrinthectomized With this technique we could destroy the saccule exclusively and leave the utricle and the canals intact, while we could also eliminate the otolith function completely by destroying the saccule and the utricular nerve with a small hook

In order to operate upon the rabbit we fixed its head by means of a clamp As anaesthesia we gave Nembutal 30 mg/kg and, if necessary, supplemented with ether An incision of 3 to 4 cm was made in the rabbits neck submandibularly After removal of the submandibular gland sideways the bulla was found along the medial side of the mandibula (fig 51) After opening the bulla with a



Fig 51 Exposure of the bulla

hisel a clear view of the middle ear is obtained (fig 52) The promontory can be emoved by means of a small hook After this a clear insight into the inner ear



Fig 52 Insight into the middle ear

s obtained permitting us to perform the manipulations we intended The utricle can be seen together with the utricular nerve (fig 53 and 54)

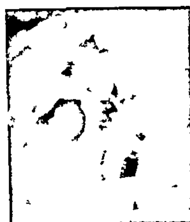


Fig 53 Insight into the inner ear The utricular nerve can be observed upon the utricle



Fig 54 Histology of the inner ear 1 Stapes 2 Facial Nerve 3 Utricle 4 Saccule 5 Ampulla 6 Cochlea

After the operation a solution of chloramphenicol was instilled before the wound was closed In order to state wether the saccule has a vestibular function or not we also tried to destroy the utricule leaving the saccule intact For this

purpose we tried to puncture through the utricle leaving the saccule intact Up till now we did not succeed in getting the intended result

In order to eliminate the function of the otoliths we also tried to dissolve them with intravenous injection of sodiumbicarbonate as described by HASEGAWA (1949 and 1955)

For our experiments about 250 labyrinthectomies in rabbits were performed (PHILIPSZOON, 1962) A number of labyrinths of animals operated upon — about 3 months after the operation — were investigated histologically *

The temporal bone was cut into 7 μ sections, orientated transversally to the cranial axis with a forward inclination of about 30 degrees For further details, also of the normal view of utricle and saccule in these preparatinons, see JAMES (1962)

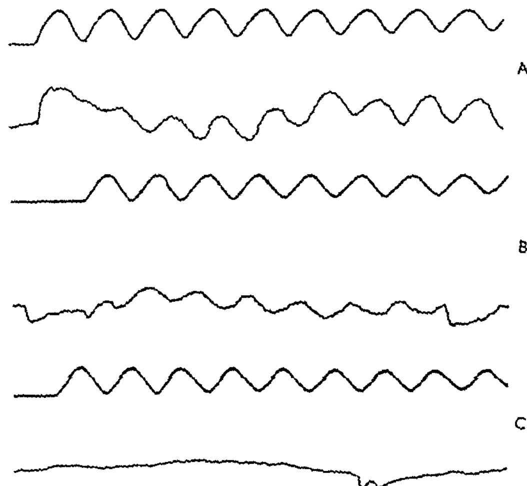


Fig. 55 Eye movements of rabbits on parallel swing
A Normal rabbit
B After unilateral labyrinthectomy
C After labyrinthectomy on both sides

* We wish to express our sincere gratitude to Dr J JAMES of the Histological laboratory (Head Prof D B Kr n) of the University of Amsterdam who investigated our rabbits histologically

RESULTS

Total labyrinthectomy

In the first place we could show that rabbits after two sided total labyrinthectomy present no compensatory eye movements any longer when submitted to stimulation on the parallel swing, whereas rabbits with one intact labyrinth still have these eye movements (fig 55)

The same result could be obtained in patients Patients who had undergone a one sided labyrinthectomy still appeared to give good compensatory eye movements, whereas a patient who was totally deaf on both sides and who did not show any reactions to the caloric and to the rotation tests, had no trace of compensatory eye movements on the parallel swing (fig 56) From these findings we may draw the conclusion that the compensatory eye movements, here described, indeed originate in the labyrinth

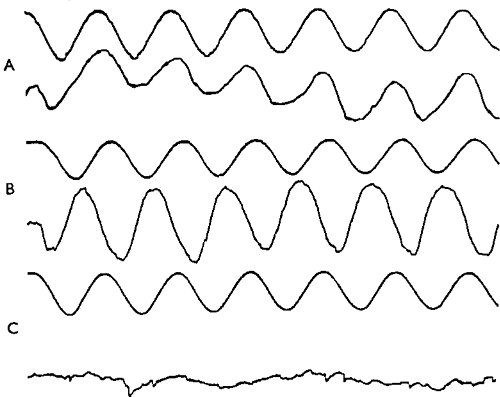


Fig 56 Eye movements of human subjects on parallel swing
A Normal human subject
B Patient after one dead labyrinth
C Patient with two inexcitable labyrinths

Destruction of the saccule

After destruction of the saccule on one side and total labyrinthectomy on the other side we still found compensatory eye movements on the parallel swing

(fig 57) and also nystagmus following angular accelerations We destroyed the saccule successfully in 10 rabbits The rabbits of these series were examined histologically. The macular epithelium could be found back in a distorted saccular vesicule, but devoid of its otoconia and gelatinous mass in which they are embed-

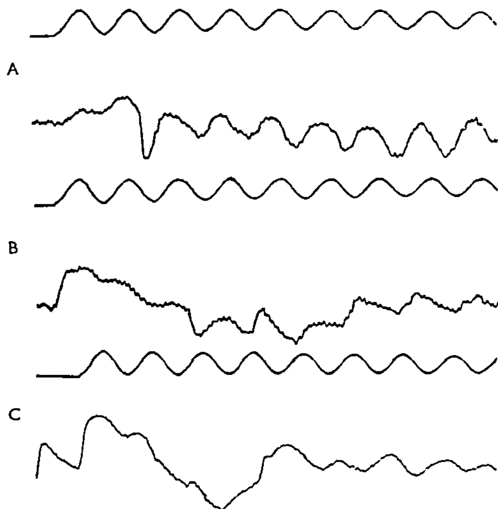


Fig. 57 Compensatory eye movements after destruction of saccule
A Before operation
B After one sided sacculus destruction
C After supplementary total labyrinthectomy on the other side

ded normally (fig 58 and 59) First we thought that this extirpation of the saccule was incomplete, but when we examined histological preparations of total labyrinthectomized rabbits, who did not show any reaction to any vestibular stimulation, we always found a similar picture of a macular epithelium without otoliths (fig 60) In our opinion we may draw the conclusion that the otoconia are essential to the function of the otolith organs Even in the old histological preparations of labyrinthectomized rabbits published by DE KLEIJN and VERSTEEGH (1935) one can discern a macular epithelium of the destroyed saccule

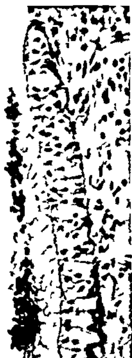


Fig 58 Normal saccule



Fig 59 Saccule macula without otoconia after saccule operation





Fig 60 Intact sensory epithelium of saccule without otoconia after total labyrinthectomy Survey and detail

Selective destruction of the otolith-organs

In order to leave the canals intact and to destroy all the otoliths we again used in our experiments the approach of VERSTEEGH. We indeed succeeded in destroying the utricular nerve with the aid of a small hook (figs. 61 and 62), while the saccule was destroyed directly. We again performed a total labyrinthectomy on the other side. In experiments on the parallel swing the compensatory eye movements proved to be absent now, whereas clear reactions on the torsion swing could



Fig. 61. Utricle with utricular nerve.



Fig. 62. Utricle with destroyed utricular nerve.

still be observed (fig. 63). We succeeded in obtaining this result in 8 rabbits.

Here we see that the canals normally respond to rotatory accelerations and not to linear accelerations. As seen above one utricle left intact can still give rise to compensatory eye movements.

With intravenous injections of sodiumbicarbonate we did not succeed in eliminating the function of the otoliths as described by HASEGAWA. Although

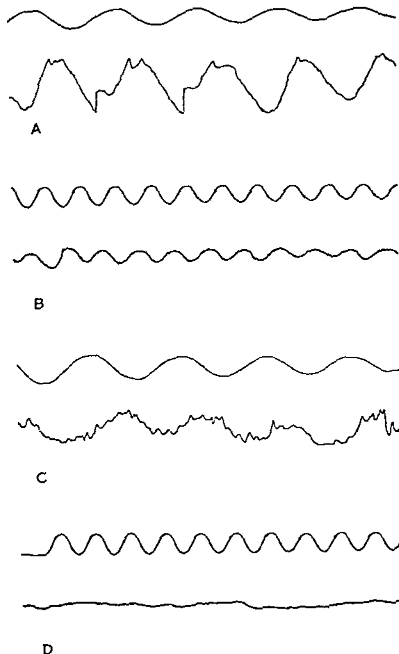


Fig 63 Selective otolith destruction A torsion swing before operation B parallel swing before operation C torsion swing after operation D parallel swing after operation

we gave rabbits the same and higher dosages than those given by this author, we did not observe any effect on the compensatory eye movements provoked by the accelerations of the parallel swing Our findings agree with those of GIACCAI and CARLE (1951) who could not observe any suppression of otolith reflexes by sodiumbicarbonate either

Another argument supporting the thesis that the otoliths are stimulated by linear accelerations and the semicircular canals by angular accelerations were the findings in a patient who had undergone fenestration operations on both ears. This patient did not react anymore to rotation in the plane of the horizontal canals, neither with nystagmus nor with a sensation of rotation, whilst a dubious nystagmus could be recorded when the patient was rotated in the plane of the vertical canals. The patient did not react to caloric stimulation and the fistula symptom was also negative on both sides. On the other hand this patient proved to have normal compensatory eye movements on linear accelerations. These findings show that for angular accelerations an intact set of canals in the plane of rotation is essential, while the reaction on linear accelerations is not disturbed by damage to the canals (fig. 64).

PURSIAINEN (1954) also found in 7 patients who had been fenestrated upon both sides the reaction to rotation in the plane of the horizontal canals to be absent.

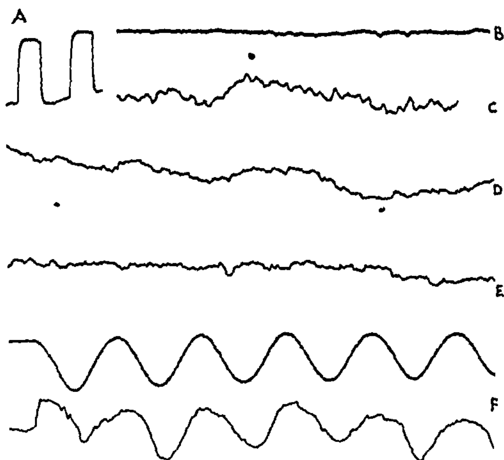


Fig. 64. Patient with both sided fenestration operation.
A. Calibration.
B. Rotation test in plane of horizontal canals: no reaction.
C. Rotation test in plane of vertical canals: dubious nystagmus.
D. Fistula test: negative.
E. Caloric test: no reaction.
F. Parallel swing test: good compensatory eye movements.

CONCLUSIONS

1 The compensatory eye movements provoked by linear accelerations on the parallel swing are caused by stimulation of the otolith organs
2 For the function of the otolith organs the otoconia are essential
3 The hypothesis of JONGKEES and GROEN, that the proper stimuli for otoliths and semicircular canals are the linear and the angular acceleration respectively, is confirmed by our experiments

SUMMARY

Investigations were performed to test whether JONGKEES and GROEN (1946) were correct when stating that the proper stimuli for otoliths and semicircular canals are the linear and angular accelerations respectively

By means of electronystagmography the eye movements provoked by linear accelerations on the parallel swing and by angular accelerations on the torsion swing were recorded

Total and partial labyrinthectomies in rabbits after the technique of VERSTEEGH (1927) were performed

After total labyrinthectomy on both sides no eye movements on the parallel swing are present any more Patients with two inexcitable labyrinths present no compensatory eye movements on the parallel swing After destruction on one side of the saccule and after total labyrinthectomy on the other side compensatory eye movements on the parallel swing can still be provoked

In a patient who had undergone a fenestration operation on both sides, no reaction was seen after rotation in the plane of the horizontal canals while good compensatory eye movements on the parallel swing could be observed

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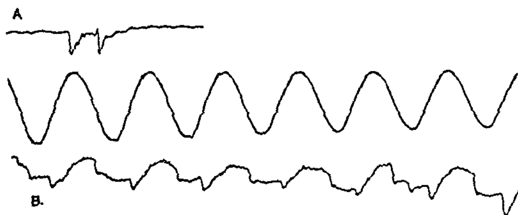


Fig. 66. A. Nystagmus of rabbit lying on a small cart in lateral position during acceleration. B. Nystagmus of a rabbit lying in the human parallel swing. More than one nystagmus beats per cycle are seen.

eyes to the left or to the right. To fix the gaze behind closed eyelids we asked the subject to look in the direction of his hand which we brought into the necessary position. In this way optokinetic influences were excluded. Again, as in the rabbit tests, we succeeded in provoking nystagmus by making the eyes more sensitive to nystagmus by a previous eye deviation (Fig. 67).

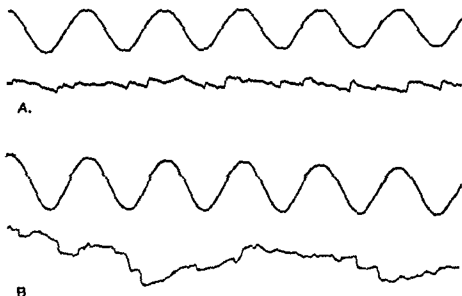


Fig. 67. Nystagmus in a human subject on the parallel swing in normal position while fixing the eyes to one side. A. to the right. B. to the left.

As the test person did not show nystagmus when he was swung when lying in side position and looking straight before him, but only when he looked in the direction of the quick phase of the excepted nystagmus, we think our hypothesis about the value of Alexander's law to be well founded (Fig. 68).

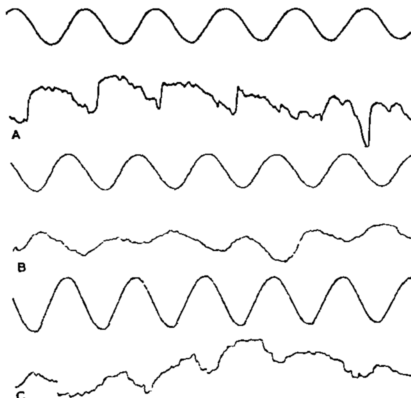


Fig 68 Eye movements of human subject in side position on parallel swing
A looking to the right
B looking straight forward no nystagmus is seen
C looking to the left.

DISCUSSION

In our opinion it is highly probable that the otoliths play an important part in the formation of nystagmus

As soon as the optomotor system is more likely to produce nystagmus (as happens when the eyes are deviated), we are able to elicit nystagmus following stimulation by linear accelerations As linear accelerations are the physiologic stimuli of the otoliths it seems probable that stimulation of the otoliths may give rise to nystagmus when the conditions for the appearance of nystagmus are made favourable

It might be suggested that the linear accelerations could have acted upon the semicircular canal system but up to now no arguments have been brought forward to sustain this hypothesis (JONGKEES and GROEN, l c)

SUMMARY

Nystagmus as a sequel of otolith stimulation or destruction had not yet been proved to exist
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The fact that in both instances the eyes are deviated laterally makes it probable that (accor

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4 *On the mode of action of linear accelerations upon the otoliths*

In labyrinthine studies great controversies have existed about the proper stimulus required for the otoliths (MAGNUS and DE KLEYN versus QUIX) Many discussions have been held about the question whether pressure or traction of the otoliths on the maculae was the most adequate stimulus for the otolith organs On the other hand BREUER, CRUM BROWN and MACH pointed to the shearing forces of the otoliths upon their underlayers as the most important stimulus

With the aid of electronystagmography we tried to find further data to solve this problem

In our experiments we studied the influence of the gravitational force upon positional nystagmus in rabbits one or two days after unilateral labyrinthectomy in the following positions prone position, right lateral and left lateral position and supine position

In order to verify whether the influence of the direction of the gravitational force acts upon the peripheral organ or upon the vestibular centres, we studied Bechterew nystagmus in the same positions

In rabbits we also studied the eye movements provoked by linear accelerations upon the parallel swing in the same positions as described above For these experiments we used both normal rabbits with a onesided labyrinthectomy after the nystagmus provoked by the operation had disappeared

JONGKEES and GROEN (1946) described sensations and eye movements provoked by means of linear accelerations presented on the parallel swing, as stated already we were able to record these eye movements electronystagmographically With the same stimulation on the parallel swing WALSH (1960) investigated the sensations of patients who had lost the function of one vestibular organ This author found the sensitivity to movements towards and away from the damaged side to be the same but it was consistently reduced when the patient lay with the damaged labyrinth downwards

Methods

Within 48 hours after labyrinthectomy we examined the rabbits in the following positions prone position, right and left lateral position and supine position

Bechterew nystagmus was also studied in the same positions within 48 hours after the second labyrinthectomy

In this part of our experiments the movements of both eyes were recorded separately, while the rabbit's head was as usual covered with a dark cloth in order to prevent optokinetic influences

RESULTS

Positional nystagmus after unilateral labyrinthectomy

We operated upon 10 rabbits 5 on the left side and 5 on the right side

As stated already (Chapter II) the direction of the nystagmus did not follow any law we could establish

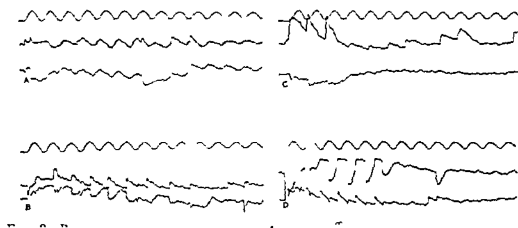
On the other hand we observed two characteristic findings in all our 10 rabbits When the rabbit was lying on the operated side the positional nystagmus always happened to be much larger than when the animal was lying on the healthy side, when the rabbit was in supine position the nystagmus was always smaller than when it was in prone position (fig 21) (see also chapter II)

Bechterew nystagmus

In 9 rabbits we examined Bechterew nystagmus We could not find any influence of the above described position upon the size of the positional nystagmus (fig 26) No difference in the size of the nystagmus could be seen between the two lateral positions In 6 rabbits there was no difference between the prone and the supine positions, in 2 rabbits the nystagmus was greater in supine than in prone position and in one rabbit the nystagmus was greater in prone position (Bos, 1962, Bos and PHILIPSZOON, 1962)

Parallel swing tests

We investigated the influence of the four described positions upon eye movements provoked by linear accelerations on the parallel swing Rabbits lying in these positions were swung sideways In 20 normal rabbits we found that the eye movements in normal position and in both lateral positions were definitely smaller than the eye movements which resulted from swinging the rabbit in supine position (fig 69) 18 times this was unmistakably true, once there was only a very small difference and in one rabbit there proved to be no difference at all



After destruction of one labyrinth this same phenomenon was still present The eye movements were larger when the rabbit lay in supine position (8 out of 9) There was again one exception But now a difference in lateral position was also visible In 8 rabbits the reaction was definitely larger when the animals lay on the side of the intact labyrinth and smaller when the lower side was the one of the destroyed labyrinth (fig 70) In one case only the reverse happened This was the same rabbit which had also a larger reaction in supine position than in prone position We repeated the experiments some weeks later and the same reactions took place again

It should be noted here that in both lateral positions the rabbits showed a nystagmus as result of linear accelerations, which are considered to be the proper stimulus for the otoliths (see above)

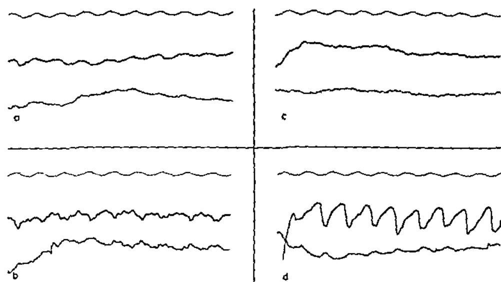


Fig 70 Parallel swing tests in a rabbit after left sided labyrinthectomy A Prone position, B On the right side C On the left side D Supine position For further legend see fig 69

As long as the rabbit remained in its normal position, we did not succeed in causing nystagmic movements of the eyes, but as soon as the rabbit was put into a lateral position, swinging of the parallel swing provoked a clear nystagmus This phenomenon is especially evident in the lower eye Both eyes showed a very marked difference in reaction If the amplitude of the swing is larger the number of nystagmus beats per half period of the swing movement increases

DISCUSSION

Before we can interpret our results we have to consider the position of the otolith organs in space (fig 71) In prone position the otoliths of the utricles are on top of the sensory cells, whilst the otoliths of the saccules are hanging sideways from the hairs of the sensory cells in the endolymphatic space, in such a way that the otoliths are lateral to the sensory epithelium When the rabbit is lying on one of its sides, the otoliths of the utricles are hanging sideways and the otolith of the lower saccule is hanging perpendicularly from the macula in the endolymphatic space, whilst the otolith of the saccule of the upper labyrinth is pressing upon the macula In the supine position the otoliths of both utricles are hanging perpendicularly and those of the saccules sideways in the endolymphatic space (fig 71 A)

From our experiments on the influence of position on the size of nystagmus after unilateral labyrinthectomy we may in our opinion draw the conclusion that, in a resting position, there is a marked difference in size of the positional nystagmus when a pressure or a traction of the otoliths upon its underlayer exists Since the alteration of the direction of a linear acceleration (the gravitational force) is the only difference in these experiments between the different positions, stimulation of the otoliths of the intact labyrinth is to be held responsible for the change in the size of the positional nystagmus In our opinion we made it highly probable in earlier experiments that the site of action of linear accelerations has to be sought in the otolith organs and not in the canals (see above)

The fact that variation of the position has no influence upon the Bechterew nystagmus excludes in our opinion the possibility that the changing of the size of positional nystagmus in rabbits after unilateral labyrinthectomy has a central origin

To get a better insight into this view we must consider the position of the otolith organs of the intact labyrinth in space (fig 71 B) When lying on the operated side, in which position the otolith of one otolithorgan (saccule) is pressing upon its underlayer, while the otolith of the other otolithorgan (utricle) of the intact labyrinth is hanging sideways, the positional nystagmus is much larger than when the rabbit is lying on the side of the intact labyrinth In the latter position the otolith of the saccule is hanging freely in the endolymphatic space, while the otolith of the utricle is hanging sideways Also when the rabbit is in prone position, the positional nystagmus is larger than in supine position

Here again we see that the otolith (now that of the utricle) is pressing upon its underlayer the positional nystagmus is larger than when the otolith is hanging

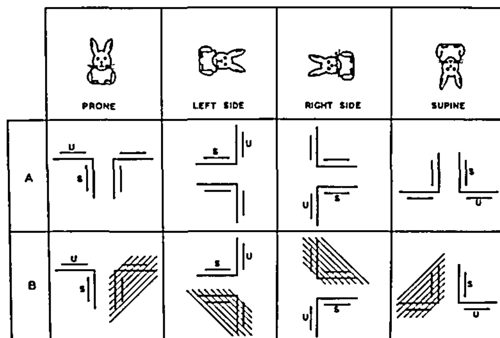


Fig 71 Scheme of the otoliths A Normal rabbit B Left sided labyrinthectomy

Our experiments seem to suggest that it is indifferent whether an otolith is hanging sideways in the direction of the abdomen or of the back (saccule) or hanging sideways in the direction of the operated side or to the side of the intact labyrinth (utricle)

Thus a difference can be stated between pressure and traction of the otoliths on their underlayers, caused by the gravitational force, upon positional nystagmus We cannot say whether pressure or traction is the most important stimulus, because we do not know whether a large positional nystagmus is due to a big stimulus from the otoliths or whether a small positional nystagmus is due to a big stimulus from the otoliths, compensating a central state of imbalance (CHILOW, 1927, LORENTE DE NÓ, 1931, KLESTADT, 1936, VAN EGMOND, GROEN and JONGKEES, 1952, JONGKEES, 1960)

In our experiments with the parallel swing we could confirm the findings and the view of WALSH (1960), who emphasized the importance of the shearing forces As mentioned we got in these experiments the largest response to the swinging when the otoliths were freely hanging in the endolymphatic space

In normal rabbits and in rabbits with one labyrinth the eye movements are bigger when they are swung in supine than in prone position, while in the rabbits with a onesided labyrinthectomy the eye movements are larger when the animal is lying on the side of the intact labyrinth than when it lies on the operated side

The explanation for these findings has in our opinion to be sought in the shearing forces

When the rabbit is in the supine position the otoliths of the utricules are

hanging freely in the endolymphatic space This makes it possible for the otoliths to exert stronger shearing forces upon their underlayer during movements than in prone position, when the otoliths are on top of their maculae In the latter position it is conceivable that the friction makes it more difficult for the otoliths to perform large excursions For the same reason the movements of the otolith of the saccule are larger in rabbits with one labyrinth when they are lying on the side of the intact labyrinth than when they are lying on the operated side

We think we may draw the following conclusions from our experiments In various positions a difference in the size of the reaction to a stimulus from the otoliths, i e positional nystagmus after unilateral labyrinthectomy, is evident when the otoliths are giving constant pressure or traction upon their underlayers as a result of the action of gravity

During movements provoked by sinusoidally linear accelerations on the parallel swing the shearing forces are maximal when the otoliths are hanging freely in the endolymphatic space The fact that there is a difference in both lateral positions in rabbits with a one sided labyrinthectomy as regards the positional nystagmus and the eye movements provoked by linear accelerations makes it highly probable that the saccule has a vestibular function

SUMMARY

10 rabbits were examined within 48 hours after unilateral labyrinthectomy

All 10 rabbits showed in the lateral positions a stronger postoperative nystagmus when they were lying on the operated side than when they were lying on the side of the normal ear

In these rabbits the nystagmus was also stronger in prone position than in supine position

These findings indicate in our opinion the following conclusions

In resting positions a difference in stimulus from the otoliths upon positional nystagmus after unilateral labyrinthectomy is evident when the otoliths are giving either constant pressure or constant traction upon their underlayers as a result of the action of gravity

During movements provoked by sinusoidally changing linear accelerations on the parallel swing the shearing forces are maximal when the otoliths are hanging freely in the endolymphatic space

The fact that there is a difference in both lateral positions in rabbits after a onesided labyrinthectomy as regards the positional nystagmus and the eye movements provoked by linear accelerations makes it probable that the saccule has a vestibular function

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5 *The effect of some drugs upon reflexes provoked by linear accelerations*

We investigated the effect of some drugs upon compensatory eye movements provoked by linear accelerations on the parallel swing (PHILIPSZOON, 1959, JONGKEES and PHILIPSZOON, 1960)

Cinnarizine clearly suppresses the compensatory eye movements in rabbits (fig 72) In human subjects we were not able to obtain a significant effect of this drug, though here also a suppressive action is highly probable (fig 73) A large intra individual variability of the eye movements on the parallel swing would require a very big number of subjects, in order to get significant results We thought it unnecessary to spend so much time to strenghten a point of view already well founded In rabbits Chlorpromazine does not suppress the compensatory eye movements on the parallel swing This confirms our results in the rotation tests

Hyoscine does not show any effect, while Nembutal only suppresses the eye movements when the rabbit got complete anaesthesia

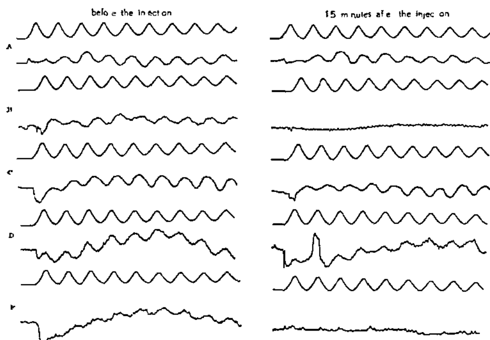
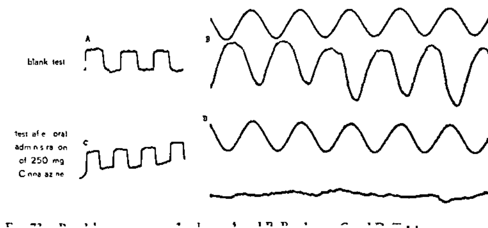


Fig 72 Parallel swing tests in rabbits The upper line represents the movements of the swing The lower line represents the eye movements A normal saline solution 10 ml, B Cinnarazine 40 mg/kg, C Largactil 8 mg/kg, D Hyoscine 5 mg/kg, E Nembutal 40 mg/kg



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THE GALVANIC TEST

PURKINJE (1820) was the first to describe that a galvanic current, flowing through the head, affects equilibrium However, till 1871 no one tried to test the vestibular system with the aid of an electric current In that year, HITZIG induced disturbances in the equilibrium when a current was passed between electrodes placed on both ears (tragus or mastoid) He observed a falling tendency in the direction of the positive electrode, and a nystagmus beating towards the negative one With a change in the direction of the current, the direction of the disturbances also changed

For our experiments we used the bipolar biauricular method

There are several theories about the site where a galvanic current takes effect in the vestibular system We will mention them only briefly

As a change in the direction of a galvanic current changes the direction of the disequilibrium, one is inclined to consider an endolymphatic movement as the cause of galvanic nystagmus, or perhaps a direct action on the sensory epithelium of the cupula, and several experiments give support to this view However, after labyrinthectomy on two sides, galvanic nystagmus can be evoked as before Thus the periphoral labyrinth is not the only place where a galvanic current could act

A next neuron that could be influenced is the ganglion of Scarpa DOHLMAN found typical reactions to galvanic stimulation of this ganglion HUIZINGA (1931) operated upon pigeons, extirpating the labyrinths and the ganglion of Scarpa, without damaging the adhering medulla After this operation, galvanic nystagmus could still be elicited by a strong current Thus it is improbable that the ganglion of Scarpa should be the only site of galvanic stimulation

A galvanic current does affect the eighth nerve, augmenting or decreasing its excitability (LOWENSTEIN and SAND, LEDOUX) We are dealing with a galvanic current hence with a continuous current (direct current) Augmenting this current gives a stronger reaction DOHLMAN, however, gives the following objections to the theory of action on the VIII th nerve It is common knowledge that a nerve muscle preparation reacts only on opening or closing of the circuit when the current is flowing continuously through the nerve, an augmentation of the current has not the slightest influence on the state of the muscle On the other hand, a faradic stimulation containing a certain number of stimuli per second, is able to induce a normal tonic contraction of the muscle Thus nerves do not react to galvanic stimulation in the way the equilibrium appears to do It is improbable that the eight nerve should be the only exception to this rule Therefore we do not regard the eight nerve as the site where galvanic current affects the equilibrium

EXPERIMENTS

As we mentioned above, we used in our experiments (Bos, 1962, Bos and JONGKEES, 1963) the bipolar biauricular method of stimulation, and recorded the nystagmus with electronystagmography A current of two mA was usually sufficient to induce a galvanic nystagmus in normal test persons This reaction was recorded during 6 minutes continuous stimulation and appeared to remain unfatigued

Galvanic nystagmus, recorded by the electronystagmograph, appeared to differ from the classic type of labyrinthine reaction, in such a way that the galvanic nystagmus did not show the abrupt alternation of the slow and rapid components (fig 74) Moreover, the galvanic nystagmus seemed to be superimposed on the



Fig 74 Galvanic nystagmus

slow phase of a spontaneous (vestibular) nystagmus of one of the test persons DE KLEYN (1920) stated that a „Dunkelnystagmus" had no relation to the vestibular system, as this ,Dunkelnystagmus" did not solve and fall into one reaction with a labyrinthine one, but simply superimposed on the slow phase of the latter nystagmus (fig 75)



Fig 75 Dunkel nystagmus superimposed upon vestibular nystagmus (DE KLEYN)

We got the impression that the same superposition took place in the combination of a spontaneous vestibular and a galvanic nystagmus

To verify this impression, we stimulated the labyrinths of normal test persons galvanically and calorically at the same time The result confirmed the idea that a galvanic nystagmus becomes superimposed upon the slow phase of a labyrinthine nystagmus

If we take DE KLEYN s point of view this would indicate that a galvanic nystagmus has no relation to the vestibular system (fig 76)

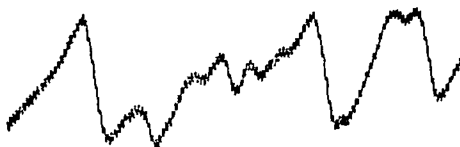


Fig 76 Galvanic nystagmus superimposed upon caloric nystagmus

SUMMARY

By means of electronystagmography galvanic nystagmus proved to be different from other kinds of provoked nystagmus

Furthermore galvanic nystagmus can be superimposed upon other forms of nystagmus (caloric and spontaneous)

It is doubtful whether galvanic nystagmus is similar to the other forms of vestibular nystag mus

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NECK TORSION TEST

In literature reference is repeatedly made to the existence of vertigo and nystagmus of cervical origin. We mention publications of BARANY (1907), MAGNUS (1924), BARRE (1925), GRAHE (1926), DE KLEYN and NIEUWENHUYSE (1927), FRENZEL (1931), HELSMOORTEL and VAN BOGAERT (1937), BIEMOND (1939 and 1940), DE KLEYN and STENVERS (1941), GARNETT PASSE and SEYMOUR (1948), GARNETT PASSE (1951 and 1953), MASPETIOL, CHARDIN and MILLARD (1954), SEYMOUR (1954), KUILMAN (1959), PHILIPSZOON (1962).

We tried to gain a better insight into the origin of this cervical nystagmus, which occurs in patients with perfectly normal labyrinths. The audiogram and the caloric test give normal results in these patients. In 1925 BARRE mentioned a „Syndrome Sympathique Cervical posterieur". This was a syndrome in which excitation symptoms of the cervical nerveplexus clearly came into prominence, such as paraesthesia and vasomotor symptoms of arms, hands and head, combined with headache, vertigo and tinnitus. DE KLEYN and NIEUWENHUYSE (1927) thought that vertigo complainst with neck ailments could be ascribed to an obstructed bloodsupply towards the labyrinths. As a result of arthrosis cervicalis the arteria vertebralis was found to be obstructed. In case of arthrosis cervicalis also an irritation of the cervical nerveplexus exists, which makes it difficult to decide whether the effect is caused either by obstruction of the arteria vertebralis or by irritation of the plexus cervicalis.

HELSMOORTEL and VAN BOGAERT (1937) described the occurrence of vertigo and nystagmus in disorders of the cervical spinal cord. They could not, however, give a clear explanation for it. In 1939 and in 1940 BIEMOND described three patients with a radiculitis cervico-brachialis. They all three suffered from a clear positional vertigo, whilst in side position nystagmus was observed. BIEMOND, however, did not seek the clue for this nystagmus in vascular disorders of the arteria vertebralis, but in an irritation of the cervical nerveplexus.

To test this hypothesis he performed experiments with rabbits. In a series of 40 animals the posterior nerve root of C_2 was cut. In two-thirds of these animals a clear positional nystagmus arose immediately after the intervention. Also after cutting C_3 and C_4 a positional nystagmus was found in some cases. BIEMOND (1962) also had opportunity to study in three patients the effect of a radicotomy of C_2 and C_3. Two of these patients were operated upon under local anaesthesia for a torticollis. After intradural cutting of the posterior nerveroots of C_2 and C_3 a very clear positional nystagmus was observed to the operated side. In the third patient, suffering from multiple neurinoma located at the posterior nerveroots of C_3 and C_4 on the left side, these were sacrificed in a partial removal of the neurinoma. During this operation no nystagmus could be observed, but immediately after awaking from the anaesthesia the patient complained of violent positional vertigo, which was clearly accompanied by nystagmus. To find an

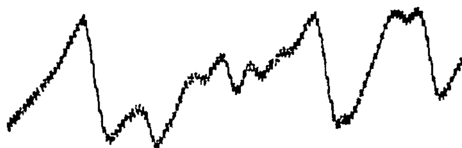


Fig 76 Galvanic nystagmus superimposed upon caloric nystagmus

SUMMARY

By means of electronystagmography galvanic nystagmus proved to be different from other kinds of provoked nystagmus

Furthermore galvanic nystagmus can be superimposed upon other forms of nystagmus (caloric and spontaneous)

It is doubtful whether galvanic nystagmus is similar to the other forms of vestibular nystagmus

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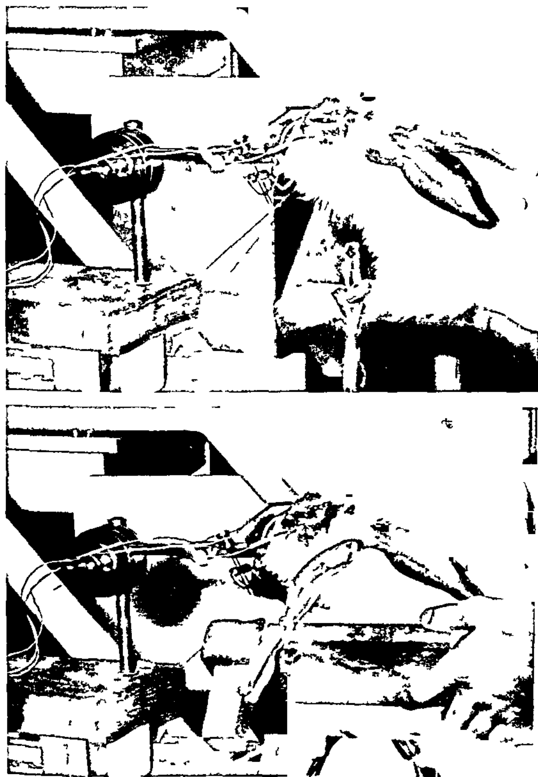


Fig 77 Tors on of a rabb t about its neck The head is kept mmob le as regards the earth by means of a clamp The trunk is rotated about a long tud nal axis

When we now performed a torsion movement of the rabbit's trunk with regard to its head round the longitudinal axis, we were able to raise and to record compensatory eye movements, which clearly passed into nystagmus when the size of the stimulus was increased (fig. 77 and 78) (PHILIPSZOON, 1962). To exclude the possibility that this neck torsion nystagmus should find its origin in the labyrinth, we also repeated this experiment in labyrinthectomized rabbits. The proof that the cervical nystagmus arises without stimulation of the labyrinth was furnished by the result of the latter experiments. Rabbits that after two sided labyrinthectomy did not show any eye reflexes on angular or linear accelerations, showed splendid compensatory eye movements and nystagmus when we applied torsion of the neck (fig. 79).

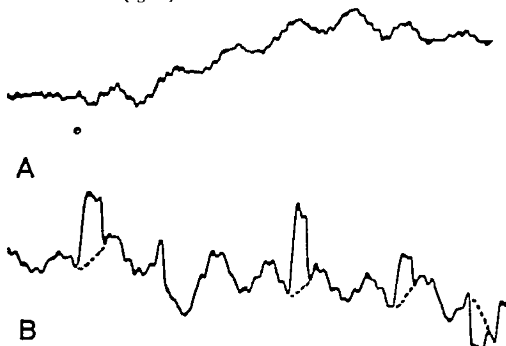


Fig. 78. A. Compensatory eye movements seen when the cervical roots are stimulated by torsion of the neck in a normal rabbit. B. Nystagmus caused by torsion of the neck in the same animal. The dotted line indicates the eye movements if the quick phase of the nystagmus would not have been present.



Fig. 79. A. Compensatory eye movements when the cervical roots are stimulated by torsion of the neck in a rabbit without labyrinths. B. Nystagmus caused by torsion of the neck in the same animal. The dotted line indicates the eye movements if the quick phase of the nystagmus would not have been present.

It must be noted that the quick phase is greater in these curves than might be expected from the distance covered by the eye during the slow phase, instantly, however, the overcompensating quick phase is compensated in its turn by another quick movement, bringing the eye back again to its normal sinus patron This is, in our opinion, another feedback mechanism on top of nystagmus We have often noticed this same phenomenon, namely, that the quick corrective phase of the nystagmus overcompensates the distance covered by the slow phase in other kinds of induced nystagmus (Fig 80) This phenomenon cannot be explained by

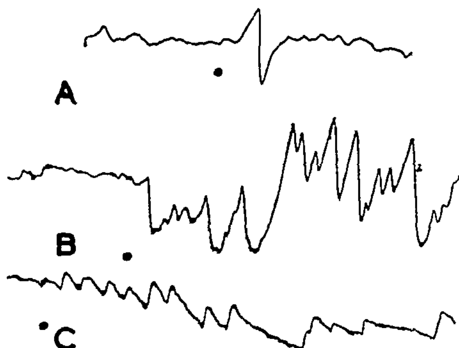


Fig 80 Examples of post rotatory nystagmus in which the first quick beat overcompensates the first slow phase A Rabbit B and C Human subjects The point indicates the moment of stopping

the response characteristic of our amplifier We used an AC amplifier with a response characteristic which is perfectly identical to that of a DC amplifier during the first 0 7 seconds (Fig 2)

After having finished our experiments we found that a similar method for provoking eye movements was described by BARANY in 1907 BARANY, however, rejected the name nystagmus for these eye movements because they were fatiguable

We also tried to provoke this neck torsion nystagmus in human beings For this purpose we placed the test persons on a torsion swing, while their heads were fixed In this way we could easily provoke compensatory eye movements and nystagmus (fig 81)

To find a counterpart for the labyrinthectomized rabbits we also examined patients with inexcitable labyrinths In two patients who had been treated with

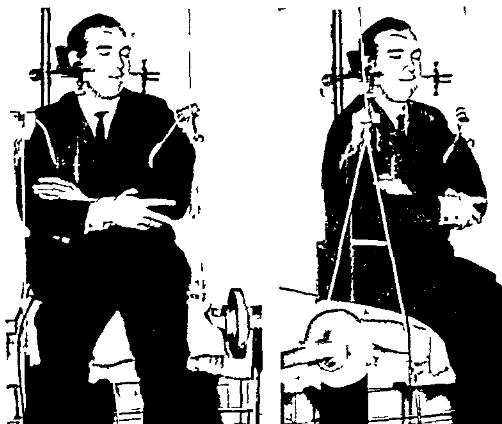


Fig. 81. Necktorsion in human subject. The subject is placed on the torsion swing, the head is immobilised by a clamp on a floorstand.

streptomycine and in one patient with a fractured skull we succeeded in provoking a clear neck torsion nystagmus (fig. 82 and 83).

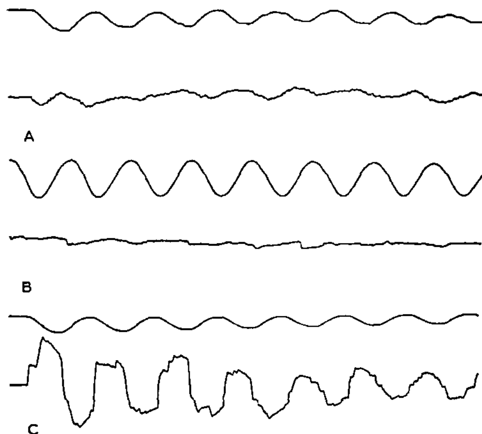
The raising of the neck torsion nystagmus may be a method to differentiate between inexcitable vestibular systems of peripheral or of central origin.

We further investigated in rabbits whether it was possible by partial or total cutting of the cervical spinal cord to abolish the neck torsion nystagmus at the same time leaving the labyrinthine rotation nystagmus intact. To prevent death by apnoea on cutting the cervical spinal cord we applied artificial respiration.

After a median incision in the neck we traced the cervical vertebral arch of C_1, which we removed. The spinal cord was exposed in this way.

We first tried to abolish the neck torsion nystagmus by only interrupting the neural conduction of the posterior part of the spinal cord by local application of novocaine.

We did not succeed. In only one rabbit we succeeded in eliminating the conduction in the posterior part of the spinal cord by partially cutting the spinal cord. In this way the neck torsion nystagmus was abolished, whilst a clear nystagmus



STREPTOMYCINE

Fig 82 Patient with peripheral labyrinthine lesion after treatment with streptomycine A Torsion swing, minimal reaction B Parallel swing no reaction C Strong neck torsion nystagmus

provoked by angular accelerations on the torsion swing, remained intact (fig 84) In 8 other rabbits we then cut the whole spinal cord immediately below the occipital foramen In 7 of these rabbits we thus managed to eliminate neck torsion nystagmus, whereas rotatory nystagmus still remained present In one rabbit the neck torsion nystagmus remained present, even after cutting In this rabbit the cutting of the spinal cord appeared to be incomplete at autopsy These findings support our point of view

To revert to the clinical significance we think it interesting to mention the following experience

As already mentioned (Bos, 1962) we often find a positional nystagmus in patients complaining of vertigo, and having normal audiograms and (calorically) equally excitable labyrinths Remarkable were, however, three fairly young patients who complained of vertigo On examination we found a normal audio

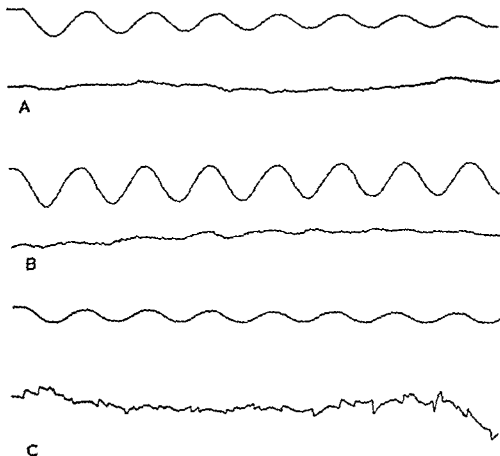


Fig 83 Patient with inexcitable labyrinths after trauma capitis A Stimulation of the semi- [illegible]

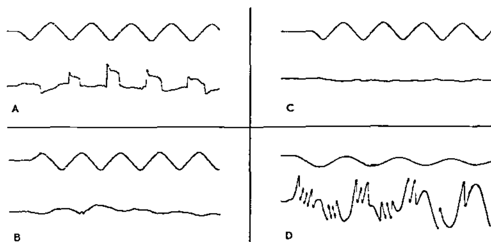
[illegible] vements, the lower the eye movements

gram in combination with positional nystagmus On inquiry these patients appeared to have practised a lot of Judo In a systematic examination of Judo-players those who had practised this sport for over 5 years, nearly all appeared to have a positional nystagmus (fig 85)

The traumas which in this sport are exerted on the neck may account for this fact Remarkable is that we practically never find any disorders of the cervical vertebra on the roentgenograms in this group, which pleads in favour of the cervical plexus-theory

In order to investigate the influence of drugs upon neck torsion-nystagmus we standardized the torsion 55° to the left and to the right, 14 swing movements per minute, lasting for one minute In normal rabbits, as well as in rabbits without labyrinths, very distinct nystagmus beats can be evoked The nystagmus of this type proves to be susceptible to suppression by cinnarizine in a quantity of 40 mg/kg body weight (fig 86)

Since this nystagmus can be provoked in rabbits and patients with dead laby-



NECK TORSION NYSTAGMUS CUTTING OF THE SPINAL CORD ABOVE C_1

A before cutting

B partial cutting

C complete cut

D torsion swing test after the operation

Fig 84 Neck torsion Nystagmus

A Before cutting very clear nystagmus movements

B After an incomplete cut slight compensatory eye movements are left

C No reaction on neck torsion after a complete cut above C_1

D Reaction on cupular stimulation (torsion swing) remained normal.

rinths, the effect of cinnarizine on nystagmus is conclusive for a central site of action of this drug

SUMMARY

Experiments were performed on the origin of nystagmus and vertigo in patients with cervical disorders and in order to verify the hypothesis that nystagmus in cervical disorders may be provoked by irritation of the posterior cervical nerve roots With the aid of electronystagmography we were able to record positional nystagmus in rabbits after cutting the posterior cervical nerve roots of C_2

We also succeeded in provoking compensatory eye movements and nystagmus in normal and labyrinthectomized rabbits by torsion of the neck, keeping the rabbit's head fixed in a clamp immobile as regards the ground to prevent labyrinthine reflexes

By cutting the spinal cord below the occipital foramen we succeeded in abolishing the neck torsion nystagmus, while the rotatory nystagmus provoked by stimulation of the semicircular canals was still present This is a strong argument for the neural origin and against the supposed vascular origin of cervical nystagmus

This neck torsion nystagmus could also be evoked in normal human subjects and in patients with inexcitable labyrinths Judokas who had practised Judo for a considerable time often appeared to have a spontaneous or positional nystagmus This could be ascribed to the cervical traumata which often occur in this sport

Cinnarizine has a suppressive effect on the neck torsion nystagmus This pleads for a central site of action of this drug

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CHAPTER VIII

THE INFLUENCE OF CINNARIZINE ON VERTIGO

After having demonstrated the suppressing effect of cinnarizine upon the vestibular system, we investigated the effect of this drug on subjective vertigo in patients (PHILIPSZOON, 1961 and 1962)

For the investigation of the effect of cinnarizine on vertigo, a double blind procedure was followed All of the patients coming from the outpatient department complained of vertigo After examination, they were given similarly appearing tablets of either placebo or cinnarizine After 1 week they were asked whether or not the vertigo had diminished Treatment was then continued with cinnarizine

In addition to a routine ear, nose, and throat examination, an audiogram and a nystagmogram were obtained Nystagmographic examinations consisted of determination of whether spontaneous or positional nystagmus existed and of performance of caloric tests The way these tests were executed is described in chapters II and III

RESULTS

Before the start of a double blind design, doses from 15 to 75 mg daily were first tried From these trials, the impression was obtained that 30 mg daily would be suitable The results of an investigation in 55 patients with vertigo are summarized in Tables I and II

The patients were divided into four (fig 87) groups according to diagnosis Group I consisted of patients with Menière's syndrome, i e , with at least two of the three objective criteria of vestibular vertigo — positive caloric examination, spontaneous nystagmus, and positive audiogram — there being no evidence that vertigo was due to otitis Group II was formed by patients with spontaneous nystagmus after an ear operation The vertigo, therefore, evidently had a peripheral cause Comparative caloric examination between both ears was of course impossible in this group Group III included patients with spontaneous nystagmus only, without anomalies in the audiogram or in the caloric test These patients almost certainly had organic disorders, of unknown origin but probably of the central nervous system Group IV consisted of patients who did not show any abnormalities in these examinations A further division can be made into group A consisting of groups I, II, and III, i e , patients with organic disorders, and group B composed entirely of group IV, i e , patients without organic disorders

The results of the examinations of the 55 patients were calculated according to the statistical method of Fisher Of the 25 patients who received a placebo, 6 experienced relief and 19 did not Of the 30 patients who received cinnarizine, 16 improved and 14 did not Statistical calculation of this result showed a onetail

ASSESSMENT OF PATIENTS

+ = positive result
— = no result

GROUP	I Ménière's syndrome	II patients with ear operations	III vertigo e causa ignota with spontaneous nystagmus	IV vertigo e causa ignota without organic disorder
PLACEBO	14 (5+, 9−)	7 (7−)	4 (1+, 3−)	0
CINNARIZINE	16 (10+, 6−)	2 (2+)	5 (3+, 2−)	7 (1+, 6−)
	vestibular vertigo (I and II)			
	group A organic disorders (I, II and III)			group B no organic disorders

Fig 87 The influence of Cinnarizine in patients with vertigo

probability level of 0.04. Since this value is below the usual confidence limit of 0.05, it was concluded that cinnarizine had a favorable effect.

Comparison in group A (organic disorders only) of the patients who received placebo and the patients who received cinnarizine showed a onetail probability of 0.004. Twenty five patients of group A were given placebo: 6 reacted favorably and 19 had no relief. Of the 23 patients who were given cinnarizine, 15 improved and 8 failed to respond to the treatment. Comparison of the patients of group A (organic disorders) who were given cinnarizine with the patients of group B (without organic disorders), all of whom received cinnarizine by coincidence, shows that cinnarizine is more effective in patients with vestibular disorders than in patients without organic disorders. Only 1 of the 7 in group B improved with cinnarizine.

Prolonged treatment with cinnarizine of the patients of groups I and II, i.e., patients with marked vestibular vertigo, resulted in reduction or elimination of symptoms in 30 of the 39 patients. Dosages varied between 30 and 120 mg daily. When the patients felt an attack coming it was recommended that they take twice the usual dose. Most of them were thus able to suppress an attack. Of the 9 patients with spontaneous nystagmus only (in group III), 4 continued treatment with cinnarizine. *In only 2 of the 7 patients of group IV (no objective symptoms)* was treatment with cinnarizine continued.

Quincke's edema was observed by the family doctor in 1 patient who had taken the drug, it disappeared spontaneously after discontinuation of therapy Cinnarizine was again given at a later time when the patient complained of severe dizziness, but no allergic reaction was seen Another patient developed urticaria after about 6 months of treatment with cinnarizine No alternation of the blood picture was seen in 8 patients who had received cinnarizine for more than 6 months Three patients complained of drowsiness, easily controlled by amphetamine, which did not suppress the favorable effect on dizziness

Later we treated over 1000 patients complaining of vertigo with cinnarizine and had good results In our experience the best dosage for most patients is 3 tablets of 20 mg a day A fairly great number of patients reacts very well to 30 mg daily, while others need 120 mg daily When patients have an attack 3 times 3 tablets a day can be given during 3 days, without unwanted side-effects

SUMMARY

In a double blind investigation cinnarizine showed a significant effect in vertigo in labyrinthine disorders

A dose of 60 mg daily gave in most patients the best results

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SUMMARY

In this survey we have tried to show the importance of electronystagmography (E N G) both for the solution of clinical and of scientific problems

CHAPTER I

After a description of the corneo retinal potential difference the way to measure it is discussed For its evaluation the recording of eye movements should be quantitatively known Careful calibration is necessary therefore In human beings this can easily be achieved by asking them to look from one known point to another and to measure the recording of the covered angle In rabbits a passive movement of the eye is used for this purpose This is forced upon the eye by a thread sutured into the cornea In the following chapters the value of E N G has been examined for the evaluation of various modes of investigation of the labyrinth

CHAPTER II

The examination of spontaneous nystagmus and positional nystagmus taught us that a speed of the slow phase larger than 6°/sec and the presence of it in more than 2 different positions suggest pathology E N G shows spontaneous and positional nystagmus much more often than examination with the unaided eye It strongly helps to differentiate between nystagmus and nystagmoid movements, which do not show the typical nystagmus pattern E N G also showed us in rabbits and in patients that no definite rules have been found about the relation between the direction of spontaneous and positional nystagmus and the site of vestibular lesions

It also helped us to find vestibular disturbances in Bell s palsy and positional nystagmus in cervical disorders

In the field of pharmacology it permitted us to record the effect of various drugs upon spontaneous and positional nystagmus and to confirm the effect of ethylalcohol, as a drug provoking positional nystagmus Pethidine did not give rise to positional nystagmus but to rough incoordinated eye movements without slow or quick phase

CHAPTER III

The caloric test with the aid of E N G is discussed The technique of Fitzgerald and Hall pike proved to be very practical The greatest advantage of E N G is that it enables the examiner to measure the speed of the slow phase of the nystagmus The limits of normal variation are given The threshold for the acceptance of pathological difference in excitability of the two labyrinths and of directional preponderance were put at twice the standard deviation both for duration and for the speed of the slow phase The difference in excitability between both labyrinths and directional preponderance should be calculated as relative values and not as absolute numbers

It appeared that the caloric test does not often give new information when the posture test and audiometry have been carefully performed Arguments are brought forward to prefer the speed of the slow phase to the duration A mechanism of memory is discussed which might influence the reliability of the measurement of the duration of caloric nystagmus

CHAPTER IV

Though E N G can be used for the recording of post rotatory nystagmus in cupulometry it enables us to use a much simpler rotatory test for clinical routine In the torsion swing test the per rotatory nystagmus can be recorded by E N G

In this way the effect of acceleration both to the left and to the right can be recorded and measured in some minutes

The effect of various drugs on the function of the vestibular organ can be investigated by using angular accelerations The suppressive effect of Cinnarizine upon per and postrotatory nystagmus is constant As Cinnarizine suppresses the electric activity of the nystagmogenic centre provoked by rotation it seems probable that its action is at least partly central

CHAPTER V

The function of the otolithic part of the labyrinth cannot easily be measured without E N G If E N G is used it becomes possible to measure the effect of linear stimulation The parallel swing is a cheap and easy instrument to provoke compensatory eye movements which can be recorded by E N G This test can be used both in rabbits and in human beings

This technique enabled us to strengthen the hypothesis that the proper stimuli for the otoliths are linear accelerations By partial destruction of the labyrinth in rabbits and by examination of patients with various lesions of the inner ear we could show that the movements of the eye caused by the linear accelerations of the parallel swing disappear after destruction of the otoliths but remain intact as long as one otolith is undamaged We could also show that linear acceleration may provoke nystagmus For its appearance a preliminary existing deviation of the eye into the direction of the quick phase is necessary

This is obtained in rabbits by putting them in lateral position and in human beings by asking them to look sideways These findings illustrate the validity of the law of Alexander which tells us that a vestibular nystagmus always becomes stronger when looking into the direction of the quick phase

Cinnarizine also proved to have a strong suppressive effect on the activity of this part of the inner ear

CHAPTER VI

CHAPTER VII

Compensatory movements of the eyes and nystagmus can be caused by torsion of the neck E N G makes it possible to record these movements They are still present after bilateral labyrinthectomy but disappear after section of the spinal cord above C_1

This neck torsion nystagmus proved to be susceptible to suppression by Cinnarizine a new proof for its central action

CHAPTER VIII

In this last chapter the results of Cinnarizine in the treatment of patients with vertigo are given A statistically significant effect on vertigo was found As a rule 3 times 20 mg a day proved to be an effective dose, which does not cause unwanted side effects

Acknowledgements

We wish to express our sincere gratitude to Mr E DE BOER Ph D for his great technical support and advises as regards the electronic problems and to Dr J JAMES (of the Histological Laboratory of the University of Amsterdam) for his kind help and histological investigations which were indispensable for our work

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S U P P L E M E N T U M 190

TASK-CONTROL OF AROUSAL AND THE EFFECTS OF REPEATED UNIDIRECTIONAL ANGULAR ACCELERATION ON HUMAN VESTIBULAR RESPONSES

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SUPPLEMENTUM 190

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CONTENT

INTRODUCTION

Wendt (1951) has indicated that habituation (a response decline) of huma nystagmus may depend upon the conditions under which the response i repetitively elicited He says visual stimuli tend to inhibit the vestibula nystagmus and with repetition these stimuli become increasingly dominan Such habituation is probably not preventable In the absence of visu stimulation he has indicated that the loss of nystagmus is preventable b keeping the subject attentive to the external surrounds and avoiding inward directed revery states

Hence in addition to specifying the importance of the conditions of elicita tion Wendt (1951) has distinguished between two *kinds of habituation* On of these is a loss of a state of attentiveness toward or interest in the surround The other and the more usual way of regarding the phenomenon refers t *a real change in the properties of the system that should be independent* o fortuitous subjective variations such as attitudinal or attentional factors

Wendt s concern with the importance of subjective states has been ampl vindicated in recent studies which have shown that simple instructions re garding mental activity can markedly modify nystagmic behavior and tha a high state of arousal attention or alertness regardless of where it is focused results in a vigorous nystagmic response (Collins Crampton & Posner 1961 Collins & Posner 1963 Guedry & Lauver 1961 Ludvall 1962 Mahoney Harlan & Bickford 1957) Further it has been demonstrated that all o the characteristics of habituation can appear as early as the first exposur of individuals to rotatory stimulation by simply instructing them to rela and daydream (Collins 1962) Such instructions literally abolish the re sponse from some subjects and markedly reduce it from most

Apparently with vision not permitted and in the absence of instructions o techniques designed to maintain attention subjects soon become relaxed an lapse into revery states Concomitantly nystagmic activity declines and ma eventually cease This type of response decline then is readily demonstrabl and equally readily reinstatable (cf Collins & Guedry 1962 Guedry Collins & Shuffey 1961)

The present study was designed to examine the effects of repeated mil angular accelerations in total darkness on human nystagmus while subject

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Study conducted with the skillful technical assistance of Kenneth J Gall and Kenneth I Swa while the author was at the U S Army Medical Research Laboratory Fort Knox Ker t ky Additional assistance in data reduction rendered by Carolyn Roulston Mary Jayne Capp ph Duchon and H Gerald Hobelmann is gratefully acknowledged

performed a number of attention-demanding tasks. The latter were employed in an effort to obviate the influence of declining alertness and to "drive" the response on every trial. Further, "habituating" stimuli were limited to CW accelerations; decelerations were sub threshold. Thus the question of whether nystagmus habituation could be directionally specific was examined. As a further point of interest, data pertaining to the subjective experience of rotation were collected to determine (*a*) if subjective habituation could occur in the absence of visual cues, (*b*) if such habituation could be made directionally specific; and (*c*) if it could occur as a result of repeated stimulation while the subject's attention was directed elsewhere.

APPARATUS AND PROCEDURE

Apparatus

Rotary The turntable has been described by Guedry and Kalter (1956) It was located in a light proof enclosure and was equipped with a slip ring system to permit recording in an adjoining room

Task stimulators A Hewlitt Packard 205A9 oscillator was used to provide stimuli for most of the tasks assigned to the subjects The oscillator was a source of both auditory and vibratory stimuli The former were presented to the subject by means of a pair of standard earphones Vibration was applied to the subject s forefinger by a Goodmans (4 ohm) Model V 58 vibrator The plastic extension of the vibrator protruded slightly through the hole in the left arm rest of the subject s chair

In all cases the oscillator frequency for the auditory stimulus was 700 cps that for the vibratory stimulus was 250 cps Stimulus intensity was maintained at a 30 dB level above the subject s absolute threshold (obtained daily) during experimental sessions A set of 3 interconnected Hunter Timers provided control over the duration of stimulus presentation

Recording All data were recorded on an Offner Type T Electroencephalograph A 1 4 sec RC time constant was used in amplification for nystagmus tracings These tracings were obtained by means of a pair of electrodes taped by the outer canthi an indifferent electrode was located on the mastoid process Subjective responses were recorded (DC) by means of a telegraph key positioned on the right arm rest of the chair Depression of the key produced a pen deflection on the recorder, release of the key returned the pen to its original base line Similar deflections were produced by the timers thereby indicating the duration of a given task stimulus Acceleration periods were recorded in a like manner

Tasks

Subjects were given a period of instructions concerning the tasks and received actual practice in all but that requiring estimation of subjective velocity In the latter case they were given several demonstrations (with the experimenter performing the role of the subject) and asked to use only vestibular information in making their judgments

Reaction time At frequent points throughout a trial subjects were presented with a tone or with a vibratory stimulus of one half sec duration Subjects were instructed to respond to the stimulus as quickly as possible by depressing the telegraph key

Temporal estimation of stimulus filled intervals Subjects were presented with a series of tones or vibrations during a trial Each stimulus lasted for a

period ranging between 0.5–6.5 sec (in 1 sec intervals). At the conclusion of a stimulus, subjects were to reproduce its duration by depressing the telegraph key for the same period of time as that occupied by the tone or the vibration.

Temporal estimation of stimulus bounded intervals. Brief (one half sec) tonal or vibratory stimuli were presented to indicate the onset and conclusion of an intervening period of no stimulation. The intervening periods (unfilled intervals) ranged in duration from 0.5–6.5 sec in 1 sec steps. Thus, e.g., a half sec tone would be followed by 4.5 sec of silence and then by another half sec tone. The subject would then reproduce the duration of the silent (unfilled) interval by depressing the key for his estimate of the length of time between the two tones. Series of these stimuli were presented throughout a trial.

Estimation of subjective velocity. Subjects were instructed in the technique of estimating angular displacement from their subjective experiences (Bekesy, 1955; Guedry & Lauver, 1961). Specifically, they were required to signal by depressing the telegraph key the onset, cessation, and each experience of 90° rotation. A warning signal was presented 10 sec prior to the initiation of an acceleration to alert the subject to the impending stimulus. When the subject signalled cessation of experienced rotation, he was instructed to remain attentive for any further rotatory sensations, however weak, which he might experience (e.g., a secondary reaction — a sensation of turning in the opposite direction without an adequate stimulus — Guedry, Cramer and Koella, 1956). Such experiences were to be reported at the conclusion of the trial. Ten sec prior to deceleration (1 min and 50 sec after termination of acceleration) a second signal was presented which notified the subject that he could close his eyes and relax until the conclusion of the trial. This task was used only in the preliminary and post tests.

Mental arithmetic. Subjects were required to do arithmetic problems consisting of silent, continuous division (Collins, 1962). A problem was assigned just before a given trial and a signal to begin work was presented 10 sec prior to acceleration. A second signal, to stop work, was presented 10 sec prior to deceleration (1 min and 50 sec after termination of acceleration). Subjects jotted down their final answer (in darkness) on a pad secured to the arm rest of the chair. They then closed their eyes and relaxed until the conclusion of the trial. This task was employed during the preliminary and post tests and for trials 1, 2, 199, and 200 during the habituation series.

Subjects

The 10 subjects were all male volunteers, experimentally naive, physically healthy, and without any past history of ear difficulties, dizziness, or unusual reactions to linear or angular motion. They ranged in age from 19–26 years with a mean of 22.8. They were cautioned to maintain normal sleeping hours, to abstain from alcohol, and to report the intake of any medicinal drugs

TABLE 1 *Procedural outline for the pre and post test trials*

Decelerations were always subthreshold (0.18°/sec²). MA refers to mental arithmetic tasks and ESV to estimates of subjective velocity. The rest period between trials 4 and 5 was 15 minutes long

	Trials								
	1	2	3	4	Rest	5	6	7	8
Direction of acceleration	CW	CCW	CW	CCW		CW	CCW	CW	CCW
Task	MA	MA	MA	MA		ESV	ESV	ESV	ESV

during the course of the experiment. Subjects were well motivated and it is unlikely that any of these factors influenced the results.

Procedure

Subjects were seated upright on a chair mounted on the rotating platform. A biteboard positioned their heads so that the horizontal semicircular canals were approximately in the plane of rotation. Earphones were worn during all trials and series of angular accelerations were administered in total darkness over 13 daily sessions. Twelve sessions were on consecutive days; the thirteenth occurred exactly 4 weeks after the twelfth.

The first, twelfth and thirteenth sessions were termed, respectively, preliminary (pre), post 1 and post 2 sessions. Each of these consisted of 8 trials (a trial is defined as a complete acceleration cycle, i.e. acceleration to constant velocity to deceleration to stop). The acceleration direction for each of these trials was alternately clockwise (CW) and counterclockwise (CCW). During the first 4 trials subjects were assigned mental arithmetic problems; during the last 4 they made estimates of subjective velocity (see Table 1).

Sessions 2 through 11 each consisted of 20 trials (habituation sessions). For this total of 200 accelerations rotation was always in a CW direction. Tasks were assigned prior to each trial (see Table 2). In all of these trials a signal was presented to the subject 10 sec prior to deceleration (1 min and 50 sec after termination of acceleration) to indicate that his task was completed and that he could close his eyes and relax until the conclusion of the trial.

All trials comprised the following: (1) 30 sec at a constant velocity of 1 rpm; (2) an acceleration of 4.5°/sec² for 13 sec; (3) 120 sec at a constant velocity of 10 rpm; (4) a deceleration of 0.18°/sec² for 333 sec to zero velocity. Rest periods of 3.5 min with the room illuminated separated the completion of a trial and the beginning of the next. Thus acceleration stimuli were separated by a total of 11.13 min. An additional 15 min rest period during which the subject was permitted to leave the turntable separated trials 10 and 11 (see Table [illegible]). Immediately prior to each trial calibrations of the horizontal displacement of the subject's eyes were made and subjects were encouraged to be attentive and accurate in the performance of their tasks.

TABLE 2. *Order of task presentation for the 200 habituation trials*

The 10 sessions each comprising 20 trials were held on consecutive days. Sound was used as the stimulus during all trials in the odd numbered sessions; vibration was used during all trials in the even numbered sessions. MA refers to mental arithmetic, RT to reaction time, and FI and BI to filled and bounded intervals, respectively.

Trials	Sessions I	II	III	IV	V	VI	VII	VIII	IX	X
1	MA	FI	BI	BI	FI	FI	BI	BI	FI	FI
2	MA	FI	BI	BI	FI	FI	BI	BI	FI	FI
3	FI	FI	BI	BI	FI	FI	BI	BI	FI	FI
4	FI	FI	BI	BI	FI	FI	BI	BI	FI	FI
5	FI	FI	BI	BI	RT	RT	BI	BI	FI	FI
6	FI	RT	RT	RT	RT	RT	RT	RT	RT	RT
7	FI	RT	RT	RT	BI	BI	RT	RT	RT	BI
8	RT	BI	FI	FI	BI	BI	FI	FI	BI	BI
9	BI	BI	FI	FI	BI	BI	FI	FI	BI	BI
10	BI	BI	FI	FI	BI	BI	FI	FI	BI	BI
Rest					15 minute rest period					
11	BI	BI	FI	FI	FI	FI	FI	FI	BI	BI
12	BI	BI	FI	FI	FI	FI	FI	FI	BI	BI
13	BI	BI	FI	FI	FI	FI	FI	FI	BI	FI
14	BI	RT	RT	RT	FI	FI	RT	RT	RT	FI
15	FI	FI	BI	BI	RT	RT	BI	BI	FI	FI
16	FI	FI	BI	BI	RT	RT	BI	BI	FI	RT
17	RT	FI	BI	BI	BI	BI	BI	BI	FI	FI
18	FI	RT	RT	RT	BI	BI	RT	RT	RT	FI
19	FI	FI	BI	BI	BI	BI	BI	BI	FI	MA
20	FI	FI	BI	BI	BI	BI	BI	BI	FI	MA

Scoring

All nystagmus records were analyzed into 3 measures: duration of response, slow phase eye displacement and frequency of beats. For the latter two, records were scored in 5 sec intervals throughout the course of the reaction. Durations were calculated from the onset of acceleration to the concluding phase of the last beat of primary nystagmus. Slow phase eye deviation was scored by summing the slow phase displacements of each nystagmic beat from peak to base line per 5 sec interval. These values were converted to degrees of eye movement by means of the calibration factor. Frequency of nystagmus was determined simply by counting the number of beats within each interval.

Of the 2080 trials conducted, only five records were not scored. Two of these were from the habituation series and, due to technical difficulties, no records were obtained. The remaining three were one pretest (Trial 1 for RW) and two posttest 2 trials (Trials 1 and 2 for EM). In these cases failure of a timing mechanism to perform properly resulted in interrupted stimulations. The obtained nystagmus was not scored for these incomplete accelerations.

RESULTS

Effects of Stimulus Repetition

Some examples of recorded nystagmus appear in Figure 1. The post-test tracings clearly indicate a brisk nystagmus in spite of the preceding 200 acceleration exposures. However, the form of the response differs from that displayed in the pre-test. The intervening series of habituating trials induced an overall decline in the amplitude of nystagmus, and an increase in its frequency during the early seconds of the response. Figure 2 and Table 3 present this relationship more clearly. For both the practiced and unpracticed directions of response, the first post-test shows a decline in slow phase output relative to the pre-test performance. A further drop is evident in post-test 2, given one month later with no intervening trials. Noteworthy differences were evident in the frequency measures for both the practiced and unpracticed directions. Specifically, during the first 20 seconds of the response the frequency of nystagmus increases from the pre- to the post-tests. However, for the remainder of the response curve the frequency shows a drop in post-test 1 and, although still below its original level, some recovery in post-test 2.

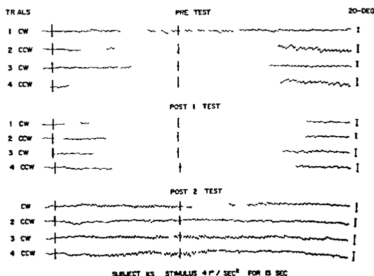
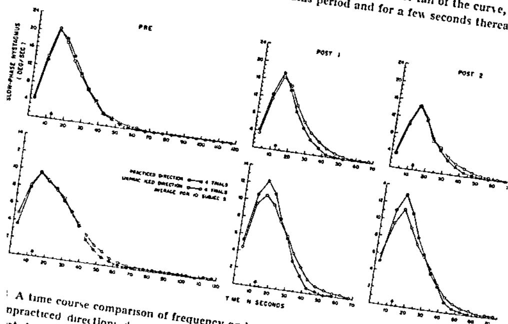


Fig. 1. Nystagmus recorded during pre- and post-test mental arithmetic tasks. Vertical bars through records demarcate the stimulus period. Five calibrations are at the right of each tracing. Note the *increased response frequency in post 1 trials following* 200 CW stimulations. Post 2 trials show no evidence of recovery to the pre-test level although one month with no intervening trials had elapsed between post 1 and post 2 tests.

FIG 2 Average nystagmus slow phase and frequency curves for pre and post test data pl
5 sec intervals An overall depression of slow phase output is evident for both the practic
unpracticed directions For frequency data a depression affects only the tail of the curve,
creased frequency response occurs during the stimulus period and for a few seconds therea



A time course comparison of frequency and slow phase nystagmus responses in practiced
npracticed directions during the pre and post tests The clearest differences appear in the
st frequency responses during and for a few seconds after the stimulus period favoring
cticed direction Compare with Figure 2

TABLE 3 *Response scores for pre and post tests*

Each total score is a mean of 8 trials and each frequency score is a mean of 4 trials unless otherwise indicated

	Subjects									
Sessions	MB	PB	LB	RB	JH	LM	HS	KS	RW	HW
					Total duration of nystagmus (seconds)					
Pre	51	52	40	48	37	61	36	54	51[a]	53
Post 1	41	42	39	34	33	47	27	40	44	50
Post 2	41	38	22	32	25	50[b]	30	41	42	47
					Total slow-phase displacement (degrees)					
Pre	510	506	336	321	333	639	231	593	610[a]	1062
Post 1	229	437	345	211	201	577	188	486	259	744
Post 2	276	282	171	238	124	516[b]	166	350	342	660
					Total frequency of nystagmus					
Pre	70	92	59	48	57	75	33	92	55[a]	69
Post 1	77	67	63	37	44	70	33	84	52	68
Post 2	91	83	49	39	49	93[b]	35	80	54	76
					Frequency of nystagmus during first 20 seconds					
Practiced direction										
Pre	34	39	35	29	31	25	19	43	25[a]	29
Post 1	54	45	45	33	35	39	31	55	32	34
Post 2	59	53	42	33	38	43[a]	30	57	25	38
Unpracticed direction										
Pre	34	49	27	25	33	30	19	48	23	29
Post 1	50	41	34	23	31	29	23	54	25	34
Post 2	56	47	32	27	30	35[a]	22	51	26	41

[a] 1 trial omitted
[b] 2 trials omitted

Figure 3 provides a direct comparison of the effects of the habituation series on post test responses in the practiced and the unpracticed directions There are negligible differences between the two directions in the pre test with the exception of the markedly longer duration for the CW direction This difference is attributable to a single subject (RB) who yielded a 2 minute response to his first acceleration Slow phase output declined for both directions in post test 1 However it apparently declined differentially relatively more for the unpracticed direction during the stimulus period and relatively more for the practiced direction during the remainder of the response The relationship between the slow phase data for the two directions in post test 2 resembles more closely the pre test although a further overall drop is evident

The frequency plots in Figure 3 are of particular interest With no significant pre test differences evident between the two directions the post tests demonstrate an increase in frequency of nystagmus during the stimulus

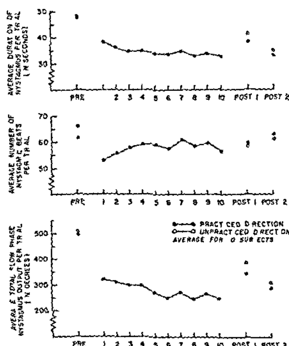


Fig 1 Average response per trial for each of the 13 experimental sessions A gradual decline during the 10 habituation sessions is evident for both slow phase and duration data an increase occurs in frequency of nystagmus Pre to post test declines in slow phase and duration of nystagmus are somewhat greater for the practiced direction overall frequency of nystagmus shows little change

period, and a depression of activity after that time This increase is clearly greater for the practiced direction where it occurs for all subjects, 6 subjects show the increase for the unpracticed direction (Table 3) One month later (post test 2), an overall frequency increase is evident for both directions, particularly during the stimulus period

Table 4 *Response scores for the pre and post tests*

Each score is a mean for 10 subjects except pre trial 1 and post 2 trials 1 and 2 (9 subjects)

		Duration (seconds)			Frequency			Slow phase (degrees)		
Trials	Task	Pre	Post 1	Post 2	Pre	Post 1	Post 2	Pre	Post 1	Post 2
					Practiced direction					
1	MA	53	40	34	67	60	60	546	305	30[illegible]
3	MA	46	38	38	64	61	61	506	376	327
5	FSA	45	37	36	57	57	64	468	330	264
7	FSA	46	38	33	62	61	68	485	317	261
					Unpracticed direction					
2	MA	50	40	34	66	56	60	527	387	316
4	MA	49	43	38	68	63	63	475	404	376
6	FSA	48	45	35	66	59	56	529	393	274
8	FSA	44	38	33	66	58	67	516	360	274

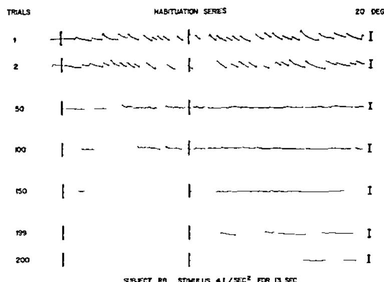
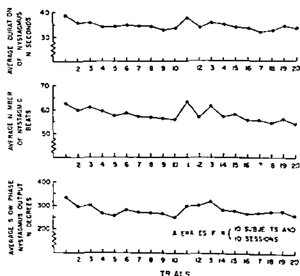


FIG 3 Nystagmus tracings obtained during the habituation series Trials 1 2 199 and 200 comprised mental arithmetic tasks The middle 3 tracings were obtained while the subject was engaged in making estimations of temporal intervals Markings are the same as in Figure 1

Plots of average total output appear in Figure 4 It is clear that some drop in the total slow phase activity and the average response duration occurs for both directions from the pre test to post test 1 An additional decline is evident in post test 2 despite the lack of any subsequent intervening stimulations For frequency measures, little change in total activity is evident for the prac



F I t Analysis of nystagmus output during the 20 daily trials Each point is an average for the 10 habituati ns Trial to-trial declines are not marked and an increased output occurs uniformly t al 11 after a 15 min rest perio l

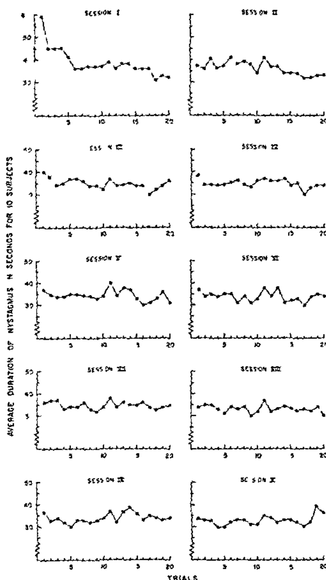


Fig 7 Trial by trial plots of nystagmus durations for the habituation series

ticed direction the unpracticed direction tends to decline by about 10 per cent Thus the overall frequency counts show little pre to post test change and thereby mask the selective effects of the habituation series on the frequency response during and for a few seconds after the angular acceleration (Figures 2 and 3)

There was no large difference evident between the output of nystagmus obtained during the mental arithmetic (MA) tasks and during those in which estimates of subjective velocity (ESV) were made However, MA trials usually showed somewhat greater output Part of this difference may be due to the fact that ESV trials were always last in the series, but they sometimes exceeded the output of MA trials (see Table 4)

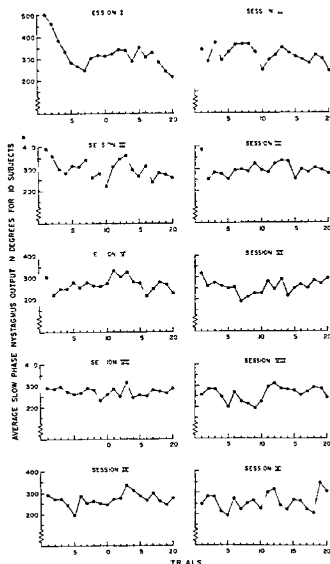


Fig 8 Trial by trial plots of slow phase nystagmus output for the habituation series

The Habituation Series

In addition to pre and post test data Figure 4 provides a session by session plot of the nystagmus data for the habituation series The points represent the average response per trial for the 20 trials in each session A fairly steady decline is evident from session to session in both duration and slow phase measures For frequency an increase occurs In all cases the maximum change is approximately 20 per cent It should be noted that the differences in output levels between pre test data and those of the habituation series are due primarily to the rather rapid decline within the first few habituation trials (Figure 5)

Fig 9 Trial by trial plots of the nystagmus frequency data for the habituation series

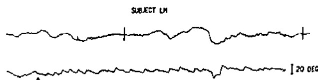


Fig 10 One of the 19 instances in which wandering eye movement and unclear nystagmus were obtained The subject was engaged in estimating temporal intervals The arrow indicates the point at which a new task stimulus was presented while he was still in the process of responding to a previous one Nystagmus was immediately restored Markings are the same as in Figure 1

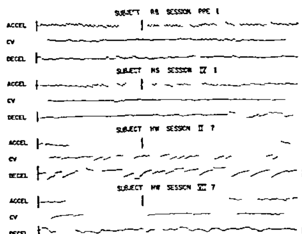


FIG 11 Some examples of secondary nystagmus and of deceleration responses The tracings are not continuous but are interrupted where the 3 dots appear Other markings are the same as in Figure 1 RB shows no secondary reaction and no directionally specific activity during deceleration Secondary nystagmus is present for both HS and HW Such responses were frequently still in progress when the period of constant velocity (CV) ended but in only some cases did they appear to be enhanced by the deceleration stimulus (as in the HW, Session II 7 record)

Figure 6 provides an indication of the course of the various response outputs over trials In this case, each point represents an average of the 10 sessions Gradual declines are evident for all 3 measures from trials 1 through 10 Increased output occurs in all cases for trial 11 (after a rest period) following which another gradual decline occurs The greatest range of trial to trial differences occurs in the slow phase data and amounts to about 25 per cent, for frequency, it is less than 20 per cent and for duration, less than 15 per cent

The average trial by trial data for each session appear in Figures 7, 8, and 9 for duration slow phase, and frequency respectively These graphs indicate that

(*a*) The most significant and striking losses in slow phase output and in duration occur within the first few trials of the first session The average response never returns to those early levels in any future trial

(*b*) Changes thereafter are much more gradual and there is no sharp, progressive trial to trial decline within a session

(*c*) A different relationship obtains for the frequency data

Subjects were well motivated and carefully instructed prior to each trial Consequently only 19 of the 2000 habituation series records showed the wandering eye movements characteristic of loss of attention In each case, these changes occured while subjects were estimating temporal durations Nystagmus was immediately re instated by simply presenting a new sound or vibratory stimulus while the subject was in the process of responding to a previous one (Figure 10) Such a procedure apparently marshalled the subject's attention processes to the assigned task

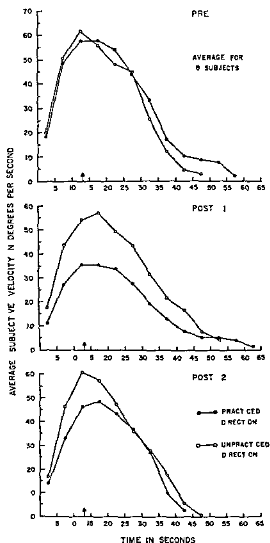


Fig 12 Subjective velocity estimated during pre and post tests Each point represents an average of 2 trials per subject Arrows indicate moment of stimulus termination Intensity of the subjective reaction is considerably diminished in post 1 for the practiced direction Post 2 shows some recovery

Wandering eye movements similar to those depicted in Figure 10 were also seen when deceleration recordings were obtained Other examples of decel eration responses appear in Figure 11 The secondary nystagmic reactions evident in the tracings of the latter figure were not infrequent occurrences Such responses were observed in 1058 of the habituation records, beginning shortly after termination of the primary reaction and, quite often, still appar ent when deceleration began On some occasions, secondary responses seemed to be enhanced by the deceleration (see Figure 11) but this was not a consistent finding

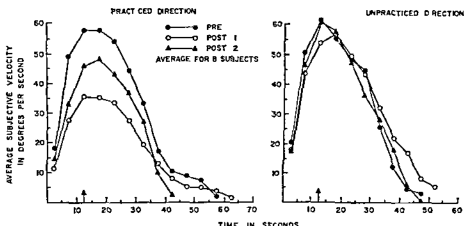


FIG 13 A direct time-course comparison of pre and post test output for the practiced and for the unpracticed directions The latter shows little or no change The practiced direction shows a substantial decline in amplitude from the pre test to post 1 Recovery is evident in the second post test given 1 month later Note that duration of the subjective response is not reduced after the 200 accelerations interposed between the pre and post 1 tests

Subjective Angular Velocity

Subjective responses were scored by measuring the amount of subjective displacement, signalled by the key pressing technique, within each 5 sec interval Since each signal represented 90° of experienced angular movement, the measurements were readily converted to degrees of displacement

Four trials each in the pre test and the two post tests provided subjective rotatory data for both CW and CCW accelerations Plotted results appear in Figure 12 for 8 of the 10 subjects For the pre test, no essential difference between the two curves is apparent However, post test 1 indicates a clear decline for the CW direction and post test 2 shows some recovery, albeit not complete after one month with no intervening stimulation From Figure 13 it is clear that the subjective impressions of angular velocity in the CCW direction were not at all affected by the 200 CW habituation trials

Data from two subjects are not included in Figures 12 and 13 Both gave abnormally long subjective responses during the pre test and, to prevent possible distortion, their data were not included in the average curves It is possible that they may have responded to nonvestibular cues or, perhaps, that they fell into a rhythm of key pressing although their sensation had diminished The latter effect has been noted in the training of subjects (F E Guedry personal communication)

DISCUSSION

Human Nystagmus Habituation

Rotation studies Griffith (1920*b*) employed 10 rotatory trials per day for approximately 4 weeks and found an average response loss in 16 subjects of 79 per cent for both frequency and duration of nystagmus His data showed a major decrease in the first few trials and he noted that, when subjects had organic disturbances or had just undergone physical exertion, nystagmus improved temporarily Griffith (1924) reported his own response to be still below its original output level some 4 years later, with no intervening stimulation However, in his study, as well as in those of Holsopple (1923, 1924) who also found nystagmus habituation, visual fixation was permitted

Dodge (1923) subjected himself to 114 rotation trials per day for 6 days He recorded nystagmus with eyes closed and reported eventual abolishment of the response to his deceleration stimulus (which was initiated while the acceleration response was going on) and a 50 per cent transfer effect when the direction of rotation was reversed He also noted that ' the rotation experiment had a soothing soporific character '

In a less extensive study, Mowrer (1937) examined the influence of vision during rotation by 12 trials alternately with and without fixation opportunities during rotation Vision was always permitted at the stop and it was here that the data were obtained He reported no significant evidence of habituation

Suzuki and Totsuka (1960) measured the duration of post rotatory nystagmus during approximately 20 trials for 4 groups of subjects Nystagmus was recorded from closed eyes and, although alertness may have been a factor in producing some marked trial to trial variability, no clear pattern of habituation was obtained

More recently, Guedry Collins, and Sheffey (1961) gave experienced subjects 10 rotation trials per day for 5 days Stimuli were 14 6°/sec² for 5 sec Odd numbered trials were entirely in darkness Even numbered trials were also in darkness with the exception of a 5 sec period (2 sec after the stop) during which visual fixation was permitted They reported a decline of nystagmus from day to day as well as within days, but noted that much of the decline appeared due to an alertness factor

Caloric studies In unilateral caloric studies, Loch and Haines (1946) reported that duration of nystagmus was unaffected when subjects were irrigated once daily for 5 or 6 days while wearing Frenzel glasses However, they noted changes in the form of the response Lidvall (1961*a*, *b* 1962) used a small number of stimuli (4–6) and found nystagmus habituation regardless of whether the interstimulus intervals were short (6 8 minutes) or long (1–25 days) Fluur and Mendel (1962*a* *b*) reported reduced nystagmus from a

series of 12 unilateral irrigations In the studies of Lidvall and of Fluur and Mendel eye movement recordings were obtained from behind closed eyes These studies differ significantly from those of rotation in that the canals on one side only are stimulated In this regard Lidvall (1961*b*) has stated that diminution of responses so elicited should not prove surprising in view of recovery patterns following unilateral labyrinthectomies

Present results The present data indicate that when subjects are kept in an alert state 200 stimulations will not abolish nystagmus to a mild acceleration applied for several seconds That the response can disappear as a function of declining alertness (and be immediately reinstated by appropriate techniques) has been demonstrated in previous papers (cf Collins 1963) and was evident in several of the records obtained here (Figure 10)

Although nystagmus in the practiced direction was not abolished the total slow phase output and the duration of the reaction were reduced by 30 5 and 19 4 per cent respectively from the pre test to post test 1 Total frequency declined only 3 2 per cent However the form of the response was strikingly changed During the stimulus period and for a few (5–7) seconds thereafter the amount of slow phase displacement declined while the frequency of the beats increased The remainder of the response became depressed for both measures and the duration was shorter These data may indicate how an apparently complete abolishment of nystagmus occurs Repeated elicitation of the eye movement response may result in increased activity of the central mechanism which controls the fast phase of the reaction True habituation in an alert subject may then come about by increased activity of the fast phase center in interrupting the slow phase drift of the eyes at earlier and earlier times so that eventually there is a very high fast phase frequency and extremely little slow phase displacement Such a mechanism could eventually completely cancel out nystagmus

These data provide no indication of whether nystagmus is differently influenced under conditions of visual fixation They indicate that in an alert subject in total darkness with the response permitted to run its course nystagmus is not easily abolished to this mild level of stimulation The previously cited studies of human habituation did not control for these factors Thus Griffith (1920*b* 1924) Holsopple (1923 1924) and Mowrer (1937) all obtained their data under conditions of fixation Although Dodge (1923) did not permit vision there are indications that alertness was a factor and in addition his acceleration and deceleration responses overlapped Declines of nystagmus obtained by Guedry *et al* (1961) were reported to be substantially affected by alertness A similar factor may account for the variability obtained by Suzuki and Totsuka (1960)

The reductions in response obtained in the present study from pre test to post test 1 did not approach the declines reported in the earlier studies Further the reduction does not have any striking directional specificity Although it is possible that the 0 18°/sec² deceleration stimulus was not completely subthreshold it seems unlikely that it would produce an almost identical amount

of response decline as a 4 1°/sec² stimulus while leaving the subjective reaction unaffected Further the subjects were permitted to relax and close their eyes prior to and during the deceleration period in a further effort to reduce any potency of the deceleration stimulus It should be noted however that since a secondary nystagmus was often in progress when deceleration was initiated some interaction of this ongoing response with the deceleration stimulus might have occurred on some trials

The second post test given after one month of rest indicates that there was little if any recovery of the nystagmic reaction A further drop in duration and slow phase activity is evident Frequency of nystagmus showed a slight overall increase These changes were true of both the practiced and unpracticed directions Hence the changes which the repeated stimulation induced are not attributable to simple fatigue nor are they readily reinstatable A similar permanency of change was reported by Griffith (1924) and Guedry *et al* (1961) It is interesting to note that a brief (15 min) rest during a series of successive rotations resulted in a temporary elevation of the nystagmic response whereas a far lengthier rest period (1 month) had no significant restorative effect

The tasks Previous short term studies of alertness and vestibular function (Collins 1962 Collins Crampton & Posner 1961) indicated that timing tasks could lose their attention value Several records obtained here showed wandering eye movements or dysrhythmia during response periods while subjects were making temporal estimations However the subjects were extremely well motivated and such occurrences were remarkably few

It is of interest that the 2 mental arithmetic (MA) trials inserted at the conclusion of the tenth and final habituation session did not restore nystagmus to its original level (Figures 4 and 5) This indicates that differences in output level between pre and post tests and the habituation series can not be accredited solely to differences in task It seems clear that MA is an extremely effective means of eliciting a vigorous long duration nystagmus to both angular acceleration (Collins 1962 Collins & Poe 1962) and caloric irrigation (Collins Guedry & Posner 1962) However the major difference between the pre test output level and that for the habituation series seems due to the rapid decline of nystagmus which occurs within the first few trials Remaining differences appear attributable to (*a*) a more vigorous response during MA and subjective rotation tasks and (*b*) fewer pre and post test trials

Use of the tasks apparently prevented the frequently reported sharp decline of nystagmus from trial to trial (e g Griffith 1920*b* Guedry *et al* 1961) That some such reduction in response occurred is clear but as Figure [illegible] illustrates it is remarkably slight is greatest from the first to the second trial and is at least temporarily reinstatable by a few minutes of rest (Trial 11) Figures 7 8 and 9 illustrate with the exception of the first session that the pattern is not at all a regular one and the within session declines are generally not great in alert subjects

[illegible] *comparative data* Nystagmus habituation has been demonstrated for

a number of infrahuman species Repeated vestibular stimulation under a variety of conditions has produced marked response declines in the pigeon (Fearing, 1926 King, 1926 Mowrer, 1934), leghorns (Fukuda Hinoki & Tokita, 1958) white rats (Griffith 1920*a*), rabbits (Dunlap, 1925, Maxwell, Burke, & Reston, 1922, Hood & Pfaltz, 1954) and cats (Capps & Collins, 1964 Collins, 1964*a*, *b*, Crampton, 1962*a* *b*, Crampton & Schwam, 1961, Henriksson, Fernandez, & Kohut, 1961, Henriksson, Kohut, & Fernandez, 1961)

The present data may be compared with results obtained from a group of 10 cats exposed to one session of 15 unidirectional rotations under acceleration conditions identical to those reported here (Collins, 1964*b*) The cat shows a marked and rapid nystagmus habituation Initially, its response is shorter in duration and lower in frequency than that of man Within a series of 15 trials, duration declines by about 50 per cent and frequency and slow phase output each by about 70 per cent The habituation occurs even when alerting stimuli are introduced (Crampton 1962*a*, Crampton & Schwam, 1961) Further, the character of the habituation process seems different from that of man There appears to be simply an overall depression of activity with the maximum loss of response occurring after termination of stimulation Crampton (1963) has referred to this as a tailoring of the cat s response to the stimulus Other data indicate that nystagmus habituation in the cat is directionally specific (Collins 1964*a* Crampton 1962*a*, Henriksson Kohut, & Fernandez 1961)

Subjective Rotation

Earlier findings Griffith (1920*b*) in addition to his reports of nystagmus decline, noted attenuation in the sensation of apparent motion which followed cessation of rotatory stimulation Under his test conditions, visual fixation was permitted

Hallpike and Hood (1953) and Hood (1960) reported a directionally specific decline in the duration of the rotatory sensation elicited from subjects with closed eyes Their technique differed from the usual stimulating conditions in that they applied a standard test stimulus (e g , 4°/sec² for 6 sec) before and after a prolonged (e g , 2°/sec² for 75 sec) constant angular acceleration The latter effected a notable decline in the post test response when both stimuli deflected the cupula in the same direction When the post test caused a cupula deflection in the opposite direction responses were normal

Guedry Collins and Sheffey (1961) had subjects estimate subjective velocity during a 5 day test series of 10 daily trials Trials were alternately (*a*) in total darkness and (*b*) in total darkness with the exception of a 5 sec period in illumination with opportunities for visual fixation The average total subjective displacement dropped by approximately 50 per cent when tests given 1 day before and 1 day after the 50 habituation trials were compared

An additional post test 9 days later showed recovery such that the amount of subjective displacement rose from 1/2 to 2/3 of its original level.

Lidvall (1961*a*, *b*) reported declines in both the intensity and duration of the rotational experience actuated by repeated unilateral caloric irrigation. However, not all subjects are able to specify a directional component to the subjective experience occasioned by such stimulation (Preber 1958).

Subjective aspects of rotation have been frequently studied in terms of the oculogyral illusion, i.e., the apparent motion of an object (usually a spot of light in an otherwise darkened room) which is actually in a fixed position relative to the subject; the object appears to move in a definite sequence during vestibular stimulation. van Dishoeck, Spoor and Nijhoff (1954) and Vogelsang (1961) have related the illusion to sensation rather than nystagmus.

Brown and Guedry (1951) noted no decline in the duration of the oculogyral illusion (OGI) as a result of a series of stimulations in total darkness, although a similar series with the target light present, and a third series with room illumination resulted in marked declines. Guedry (1950) found a trial to trial attenuation in the duration of the illusion by alternating trials in total darkness with those in full room illumination. Later, he reported declines in duration of the illusion which were specific to the direction of nystagmus when room illumination was introduced (Guedry 1953*a*, *b*). These studies emphasized the importance of visual fixation in habituation of the OGI response.

In a later study, Guedry and Ceran (1959) employed prolonged, constant angular accelerations of low magnitudes. Although their primary concern was in the decline of subjective velocity (using a target light as a reference point) *during* an extended stimulus period, they also noted a reduction in subjective velocity as a function of stimulus repetition. The reduction of the subjective response *during* a single prolonged stimulus (Guedry & Beberman 1957, Guedry, Cramer & Koella 1958, Guedry & Lauver 1961) represents an adaptation process which probably differs from that under consideration here.

Present results. The data obtained for subjective rotatory experiences provide a clear indication that the decline in the sensation of angular movement is specific to a practiced direction of stimulation. The 200 CW habituation trials produced virtually no change in the magnitude and duration of the subjective reactions to CCW acceleration. However, for the practiced direction, total subjective displacement declined by about 37 per cent and peak subjective velocity by about 39 per cent from the pre-test to post-test 1. After one month without intervening rotation trials, recovery was evident. Total subjective displacement was now only 27.5 per cent less and peak subjective velocity only 16.5 per cent less than the pre-test values. A decline in rotatory sensation with repetition of stimulation and a subsequent indication of recovery after several days of rest was also reported by Guedry, Collins & Sheffey (1961).

In addition to the importance of demonstrating that the subjective decline can clearly be made directionally specific and that visual fixation is not a

necessary condition for such an occurrence these data provide an indication that subjective vestibular habituation may occur in the absence of attending to the rotational stimulus Reports from the subjects seemed to indicate that they were generally unaware of rotatory sensations during the habituation series and were attending instead to the assigned tasks

Some Related Studies

Occupation induced habituation The performance of individuals in certain occupations would seem to require at least some forms of vestibular habituation Figure skaters for example undergo extremely vigorous rotator experiences with no apparent disorienting effects Examination of such people in the laboratory is reported to indicate a lack of both vertigo and nystagmus when they are stimulated either by rotation or by caloric irrigation (McCabe 1960)

Since World War I the study of vestibular habituation has been closely related to aviation medical problems Indeed questions concerning the vestibular function of pilots provided the impetus for many of the early studies Recent investigations have examined groups of pilots to determine the effects of flying experience on their responsivity to vestibular stimulation Aschan (1954) employed rotational stimuli and reported lower than normal values for both sensation and nystagmus durations in a group of Swedish fighter pilots There was no apparent directional specificity for the reduced sensation but directional differences in nystagmus appeared related to the direction in which the pilot preferred to roll his plane Long periods of reduced flying activity resulted in a normalization of the vestibular response particularly with respect to nystagmus

Caporale and Camarda (1958) examined 4 acrobatic jet pilots with rotation tests of nystagmus They noted a vestibular asymmetry in each pilot that was correlated with the lateral position of the man in the acrobatic V formation most frequently used

Preber (1958) tested a group of trainee pilots before and after flight training He divided them into 3 groups (no airsickness airsick once or twice severely airsick several times) on the basis of a questionnaire given after 4–6 months in the course In reexamining his vestibular findings obtained before training began he noted large differences between the no airsickness and the severely airsick groups The latter showed greater maximum slow phase eye speed and longer durations of sensation to both rotation and caloric irrigation A follow up examination of the severely airsick group after they had adapted to the flying situation and had shown no further symptoms indicated that their sensations of turning and the maximum eye speed of nystagmus had declined for the rotatory and caloric tests

Groen (1962) mentions a study by Krijger which indicated that both the sensation and the nystagmic response to rotation were inhibited in experienced test pilots when their data were compared to those of a control group After several weeks of flying inactivity their responses returned to normal

Observations during an aircraft maneuver were made by Dearnaley, Reason and Davies (1962). Subjects reported the duration of the vestibular after sensation following one minute long 45 degree banks. Duration of the sensation was markedly shorter for experienced pilots than for trainees whether their eyes were closed or visual references were available.

The studies cited above indicate that the repeated vestibular stimulation occasioned by some occupations results in a recoverable modification of the vestibular response. That the reduction of sensation was not found to be directionally specific (Aschan 1954) while that of nystagmus was (Aschan 1954, Caporale & Carmarda 1958) and that recovery of the oculomotor reaction occurred after several weeks of inactivity (Aschan 1954, Groen 1962) differ from findings in the present study. However, several reconciliating explanations are possible. (1) Only duration of the sensation was reported in the cited studies. Present data show little effect on the duration but a marked effect on the intensity of the subjective reaction. Further, the pilots were exposed to angular movements in more than one direction. This may have had an equalizing effect. (2) Habituation of the vestibular response for these occupational groups is occasioned by efforts to overcome sensations which intrude on performance. Further, opportunities for visual fixation are present. It is possible that the mechanism of habituation differs depending upon whether combinations of intention and visual references are present, or whether the reaction is simply elicited repetitively (Guedry 1964). The latter condition may more accurately represent Hood and Pfaltz's (1954) "non meaningful stimuli" than does the former.

Unusual vestibular stimulation. Responses to passive rotation about the center of a vertical axis with the head held in a fixed position, characteristic of the test situation reported here, differ markedly from the vestibular reactions elicited as a result of head movements during constant rotation. The subjective experience produced by such stimulation can be extremely uncomfortable and disorienting, and the nystagmic reaction comprises both horizontal and vertical components. Habituation of these Coriolis phenomena, both subjective and ocular, was noted by Guedry and Montague (1961), while Graybiel *et al.* (1961) reported a reduction in the oculogyral illusion as a result of repeated head movements in a rotating room.

Analysis of Coriolis nystagmus habituation indicated that a compensatory response, opposite in direction to the responses elicited as a result of head movements in the rotating room, was built up over time to counteract the disorienting reactions and produce a state of adaptation (Guedry & Graybiel 1962). Further studies indicated that when head movements were restricted to a particular quadrant, there was no transfer to the unpracticed quadrant (Guedry, Graybiel & Collins 1962, Guedry, Collins & Graybiel 1964).

The vestibular habituation attendant to adapting to head and body movements in a constantly rotating environment appears different from the mechanism by which nystagmus was reduced in the present study. However, there are notable differences in the experimental conditions. In the Coriolis studies

all 3 pairs of semicircular canals were stimulated otolith and proprioceptor activity was marked visual fixation was permitted and as in the occupational studies cited above intention was involved as the subjects tried to inhibit the uncomfortable reactions

Overview

Data obtained in the present study indicate that a bidirectional decline in nystagmic output occurs in man as a result of repeated unidirectional angular accelerations in total darkness Nystagmus however is not readily abolished to these mild levels of stimulation if subjects are maintained in an alert state Rather the character of the response becomes altered apparently by increased activity of the central mechanism which controls the fast phase of the reaction This modification of the central nervous system is not capricious the response shows little or no recovery toward its original intensity and form after a month of rest

The decline in the subjective rotatory experience has four aspects of interest (1) Whereas nystagmus was bidirectionally modified the reduction of the *sensation of rotation was specific to the direction of the habituation trials* (2) The reduction occurred in the absence of visual references (3) The reduction apparently occurred without the attention of the subjects being focused on their sensations of movement (4) A pattern of recovery of subjective intensity was evident after 4 weeks with no intervening stimulation

It is possible indeed even likely that the reduction of the subjective reaction might have been greater had appropriate visual stimuli been employed It has been demonstrated that under certain conditions visual information can obviate the sensation of movement while nystagmus is relatively unaffected (Guedry Collins & Sheffey 1961) The present study provides additional confirmation of the separate nature of the oculomotor and the subjective aspects of the vestibular response

An evaluation of this and other studies (cf Crampton 1962*b*) seems to indicate that no single term such as habituation response decline central suppression or adaptation can completely connote the effects of repeated stimulation upon vestibular function Rather there is more than one type of rotational habituation to use the classical term and the types apply to both sensation and nystagmus They may also differ from the effects of repeated unilateral caloric stimulation (Huur & Mendel 1962*a* *b*)

One of these types as Wendt (1951) noted refers to alertness or arousal If a subject is not in an alert state nystagmus output shows a marked reduction and in some cases no nystagmus may be present Such a state probably occurs with repetition of stimulation as the subject becomes habituated to the environmental conditions including the stimulus and the novelty of the situation This type of habituation appears to influence both the slow and fast phases of nystagmus although the latter activity appears more significantly reduced (Collins & Guedry 1962) The subject who is not alert may also have no subjective rotatory experience

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SUMMARY

Ten subjects were each exposed to a habituation series of 200 mild CW accelerations in total darkness while performing a number of attention demanding tasks Decelerations were sub threshold Preliminary and post tests indicated that slow phase nystagmus and duration of the ocular response declined bidirectionally as a function of the habituation trials That the total reduction in response was not as great as that reported in earlier studies seems due to the task control of alertness A marked change in the form of the response occurred Specifically stimulus repetition produced an increase in frequency of nystagmus during the stimulus period and for a few seconds thereafter The remaining tail of the response showed an overall depression These changes although greater for the practiced direction were evident for both CW and CCW stimulation

Measurements of subjective velocity were obtained during several pre and post test trials but never during the habituation series A decline in the intensity of the sensation to CW acceleration was produced by the habituation series but the subjective experience to CCW acceleration was unaffected Thus a directionally specific decline in the subjective vestibular response occurred in the absence of attending to the rotatory sensation in the habituation trials and without visual cues

A second post test given after one month with no intervening stimulation showed little or no restoration of nystagmus However the subjective reaction demonstrated a clear albeit incomplete pattern of recovery

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BY

CARL-MAGNUS ENEROTH

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Contents

Introduction

A characteristic feature of tumours of the parotid gland is a pronounced variation in the histological picture Although there is an extensive literature on these tumours, no large operative series was described until the early nineteen-fifties Consequently, great difficulties were encountered, before this time, in correlating various histological structures with the corresponding clinical course in a sufficient number of cases to permit separate types of tumour to be distinguished This implied that, until the beginning of the nineteen fifties, the classifications of parotid tumours given in the literature had to be based on diffusely delimited groups These groups subsequently proved to contain a number of different types of a varying grade of malignancy This naturally led to considerable uncertainty with respect to the prognosis and treatment both of the various types of tumour and of the individual tumours This uncertainty in evaluating the malignancy explains the widespread acceptance, following publication of Ahlbom's monograph in 1935, of the term "semi malignancy" introduced by Masson (1924)

Ahlbom's material was studied histologically by Reuterwall, who set up a system of classification based on the types of tumour described up to 1935 This was to be of great future importance, since it was the first time a histological classification had been made of a large series of mucous- and salivary gland tumours — totally 214, of which 162 were located in the parotid gland

The reason why no large operative series was reported until the early nineteen-fifties was partly the rarity of parotid tumours, and partly the former relatively low incidence of operation on these tumours Tumours of the salivary glands are stated to comprise less than 3 per cent of all tumours (*e g* Ahlbom 1935, Hellwig 1945, Marshall & Miles 1947, Pack & Ariel 1959) and about 75—85 per cent of salivary gland tumours are located in the parotid gland (Pack & Ariel, Diamant *et al* 1963) The comparatively low incidence of operation on parotid tumours until the late nineteen-forties is, probably, due to the fact that the high rate of recurrence and of damage to the facial nerve discouraged surgical intervention to some extent As late as 1933, McFarland actually stated that operation of tumours of the parotid gland was unnecessary, and in 1942 he emphasized that the postoperative prognosis could not be determined with greater accuracy than by tossing a coin

However, during the nineteen-forties parotid tumours started to be operated on to an increasingly great extent This was due to improvements in the surgical technique owing to better knowledge of the facial nerve, whose exposure after its exit from the stylomastoid foramen was described by Bailey (1941), among others Concurrently, tumour therapy began to be centralized in a successively

larger number of places. This implied that larger operative series could be collected than ever before, and the premises were created for classifying characteristic *histological structures as separate types of tumour.* Thus, in 1945—1954, several types of tumour were differentiated from earlier diffuse conceptions. One of the consequences was that the group of mixed tumours became more distinctly defined histologically.

On the basis of the types of tumour defined histologically up to 1954, Foote & Frazell (1954) presented a classification of parotid tumours that was more differentiated than any earlier one. Despite this, their classification has not become widely *adopted outside the U.S.A. This is because it has not been possible to verify its* clinical value, owing to series that are too small, too heterogeneously treated, or insufficiently analyzed. Several of the types of tumour in Foote & Frazell's classification — *e.g.* mucoepidermoid carcinoma and acinic-cell carcinoma — are still regarded in many classifications as not being independent types, but are assigned to various collective denotations (Redon 1960, Willis 1960, among others). But even in most of the classifications in which these types of tumour are considered *to be independent,* the concept of semi-malignancy persists. Thus, Rauch (*1959*), Glaser (1962), Hellner (1962) and Morehead (1962), among others, denote about 75 per cent of all parotid tumours as semi-malignant.

It is evident that there is still great uncertainty regarding the histological classification and prognosis of tumours of the parotid gland. Consequently, a definite need exists of a classification based on histologically well-delimited types of tumour, from whose microscopical features clinical conclusions can be drawn.

The main object of the present investigation was to test the justification of the term semi-malignancy, and to ascertain whether histologically delimited types of parotid tumour can be classified as definitely benign or malignant.

CHAPTER I

Case Material

The present investigation is based on an analysis of 864 tumours of the parotid gland, involving 802 patients, operated on at the Department of Otolaryngology, Karolinska Sjukhuset, during the period Jan 1st, 1950 to Dec 31st, 1962 inclusively. The reason why such a large number of the relatively rare parotid tumours were operated on at a single clinic, during a comparatively short period, is that tumour treatment has become centralized to Karolinska Sjukhuset, as a result of cooperation with Radiumhemmet.

Starting in 1950 parotid gland surgery was transferred from the Department of Surgery, Karolinska Sjukhuset, to the Department of Otolaryngology. This is why totally only 28 tumours of the parotid gland underwent surgery at the latter department from 1940—1950, as compared to 864 during the 1950—1962 period.

The 864 tumours comprising the material are denoted as primary, secondary and recurrent tumours, respectively. By primary tumour is meant a tumour that had never been operated on earlier, whereas a secondary tumour is one that had been operated on at another clinic before operation was performed for the first time at

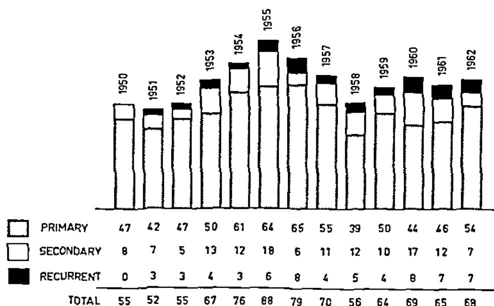


Fig 1 Primary secondary and recurrent tumours annual distribution in the present material

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It is evident that there is still great uncertainty regarding the histological classification and prognosis of tumours of the parotid gland Consequently, a definite need exists of a classification based on histologically well-delimited types of tumour, from whose microscopical features clinical conclusions can be drawn

The main object of the present investigation was to test the justification of the term semi malignancy, and to ascertain whether histologically delimited types of parotid tumour can be classified as definitely benign or malignant

CHAPTER II

Methods

Histological Study

During the nineteen-fifties, the material was largely classified according to a nomenclature in which the tumours defined in the U.S.A. in 1945—1954 as mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma and benign lymphoepithelial lesion had not yet become accepted as separate types. This implies that these types of tumour were, as a rule, originally classified under diffuse collective headings, *e.g.* mixed tumour or cylindroma.

I considered that if any clinical conclusions were to be drawn from the histological structure of the parotid tumours, it was necessary to re-examine the whole material histologically, and to re-classify it according to the modern, more differentiated nomenclature described in Chapters IV—XIV.

The prerequisites for a histological re-examination of the whole material existed, since it is archived at the Institute of Radiopathology, Radiumhemmet. The tumours are embedded in paraffin and, in addition, there are generally several cut sections of each tumour.

The histological re-examination was made without reference to earlier microscopical reports or case records, so that I would not be influenced by earlier diagnoses, or the clinical course of the tumours. In some cases, it was difficult to evaluate the microscopical picture in the already sectioned specimens, and in these cases new sections were cut from the paraffin embedded tumour. After this study, the histological data and the new diagnoses, based on the characteristic features of the types of tumour described in Chapters IV—XIV, were recorded.

To check the results of the histological re-examination, the whole tumour material was studied once more, by another examiner (Ass. Professor G. Moberger, Institute of Radiopathology), who was not aware of my results. This time as well, the examination was made without access to the primary histological diagnoses or data on the clinical course.

Clinical Follow-Up Study

The clinical follow-up study was based on 543 tumours of the parotid gland (512 patients) operated on during the period Jan. 1st, 1950 to Dec. 31st, 1957 inclusively.[1] It was continued until Dec. 31st, 1962.

[1] To increase the number of more unusual, malignant types of tumour, 3 patients operated on in 1958 have been added to the series (2 cases of mucus-producing adenopapillary carcinoma and 1 case of trabecular adenocarcinoma).

The postoperative follow up examinations of the patients were made partly at Radiumhemmet and partly at their local hospital, and the data on the clinical course were noted in the case records at Radiumhemmet, generally at intervals of 3, 6 or 12 months In 12 cases in which the patient did not attend for follow up examination, information was obtained from the Parish Registers so that it could be established whether or not the patient was alive Another few patients emigrated from Sweden, and discontinued follow up examinations for this reason

Apart from some benign tumours (*e g* neurinoma or neurofibroma) and tumour like lesions (*e g* cyst or benign lymphoepithelial lesion) about 98 per cent of the tumour material from 1950—1957 underwent regular follow up examinations for *more than* 5 years

The 5 year results of the clinical follow up study are recorded in tabular form for each type of tumour In addition any metastases and deaths from the tumour disease are given for the whole observation period which ranged from 5—13 years The clinical follow up study was based on the case records of Radiumhemmet whereas other data *e g* personal data symptoms and signs of the tumour and therapy were taken from the case records of both Radiumhemmet and the Department of Otolaryngology Since the case records of two different clinics were scrutinized most of the clinical data could be compared and checked before they were registered on the punch cards on which all the histological data were already recorded It was not until this had been done that a correlation study was made between the histological features of the various parotid tumours and their clinical features

Statistical Methods

The prognostic implications of the various histological criteria of the parotid tumours were investigated by studies of the rate of local recurrence metastasis, mortality and survival in the different types of tumour in the material To permit reliable conclusions to be drawn from the clinical follow up study this investigation was based on the part of the case material followed up for at least 5 years

The effect of various histological features of the mixed tumours on the recurrence rate was difficult to ascertain because of the small number of local recurrences in relation to the number of operated tumours A possible difference in the recurrence rate was calculated by conventional statistical methods and tested by a χ^2 test However in view of variations both in the composition of the material (primary and secondary cases) and in the radicalism of the surgical intervention, no definite conclusions can be drawn from the recurrence rate Consequently when determining the malignancy of the various types of tumour I ascribed the greatest importance to the metastasis and survival rate

The 5 year survival rate for each type of tumour is given both as the *observed* rate and as that calculated after correction for the deaths in intercurrent diseases The observed 5 year survival rate denotes the number of surviving patients as a percentage of the total number of patients followed up during a 5 year period

In determination of the observed survival rate, the mortality in intercurrent diseases plays a certain role, particularly with a long observation period. However, in the present investigation, the observation period was not extended for any lengthy time, so that the mortality in intercurrent diseases did not affect the 5-year observed survival rate to any great extent. Nevertheless, to permit the grade of malignancy of the various types of tumour to be evaluated and compared with greater certainty, I also calculated the 5-year survival rate with correction for the mortality in intercurrent diseases. This calculation was made with the method described by Nohrman (1949) and Hultborn (1952), among others, based on the annual mortality in the tumour disease. The following symbols were used:

a = number of deaths from intercurrent diseases

b = number of deaths from parotid tumour

c = number of survivals observed at the end of the period

L = number of survivals at the end of the period calculated on the annual mortality in the tumour disease (q)

The mortality in the tumour disease (q) for each year is calculated from the formula

$$q = \frac{b}{\frac{a}{2} + b + c} \qquad (1)$$

which implies that patients who die of an intercurrent disease are assumed to be exposed to the risk of death from the tumour disease during half of the year in which they died.

The number of survivals, after correction for the mortality in intercurrent diseases after n years is calculated from the formula

$$L_n = N(1 - q_1)(1 - q_2) \ldots (1 - q_n) \qquad (2)$$

in which N is the number of patients observed.

In the following, the calculated 5-year survival rate after correction for the mortality in intercurrent diseases is denoted only as the *calculated 5-year survival rate* as distinguished from the *observed 5-year survival rate* which does not take into account the mortality in intercurrent diseases. The calculated 5-year survival rate is, actually, the best expression of the grade of malignancy of a tumour. Consequently it is used for designation of, and comparison between the grade of malignancy of the various types of tumour in the material.

CHAPTER III

Classification

Primary Classification

The material was primarily classified according to a nomenclature in which the group of mixed tumours in particular is diffusely delimited, and constitutes a collective term for several different types of tumour With the diagnosis of such tumours as mucoepidermoid carcinoma, adenoid cystic carcinoma and acinic cell carcinoma as separate types in the late nineteen forties and early nineteen fifties, the mixed tumour group became more distinctly defined from the histological point of view This implied that the primary classification of the present material became increasingly differentiated To illustrate this, the primary diagnoses in the material are listed during two periods, i e, 1950—1957 and 1958—1962 The division into these periods was done in view of the fact that the follow up study was based precisely on the operative material from 1950—1957 The distribution of the primary diagnoses during these two periods, as well as in the whole operative series, is shown in Table 1

In a comparison between the incidence figures in 1950—1957 and 1958—1962, some figures in particular illustrate the tendency to an increased differentiation during the latter period First and foremost there is the percentage increase in the mucoepidermoid carcinoma, adenoid cystic carcinoma and acinic cell carcinoma groups The two latter types were not, in fact, diagnosed at all before 1958 That these types of tumour were formerly classified mainly as mixed tumours is evident

Table 1 Present material distribution of the primary diagnoses during different periods

Period	1950–1957	1958–1962	Total	
No of patients	512	290	802	
	%	%	No	%
Mixed tumour	82 0	68 3	618	77 0
Papillary cystadenolymphoma	4 6	7 6	46	5 7
Oncocytoma	0 2	0 7	3	0 4
Misc benign tumours	8 9	8 3	70	8 7
Mucoepidermoid carcinoma	2 3	4 1	24	2 9
Adenoid cystic carcinoma	0	2 4	7	0 8
Acinic-cell carcinoma	0	4 8	14	1 7
Misc malignant tumours	1 7	3 8	20	2 5

Table 2 Mixed tumours primary grading of the malignancy during different periods

Period	1950—1957	1958—1962	Total
No of tumours	420	198	[illegible]
	%	%	%
Benign	34 8	59 [illegible]	42 [illegible]
Semi malignant	57 1	35 3	[illegible]
Malignant	8 1	5 1	[illegible]

from the marked decrease in the diffuse mixed tumour group (from 82 [illegible] 68 per cent), following the distinction of separate types of tumour [illegible] modern American nomenclature Before this distinction no definite [illegible] can have been drawn about the malignancy of the diffuse [illegible] mixed tumours This is apparent from the fact that such a large [illegible] the tumours primarily diagnosed as mixed tumours were denoted as [illegible] *i e*, of uncertain malignancy (Table 2)

Table 2 shows that the incidence of semi malignant mixed [illegible] from about 57 per cent in 1950—1957 to about 35 per cent in 19[illegible] implies that the evaluation of the malignancy of tumours primar[illegible] mixed became more certain in the latter period The probabl[illegible] increased differentiation of the histological diagnoses in recent yea[illegible] in Table 1 Thus, the earlier exceedingly diffuse mixed tumour [illegible] more clearly defined histologically As a result it became ea[illegible] malignancy in this group Despite this in 1958—1962 a large [illegible] mixed tumours (> 35 per cent) were still denoted as semi mal[illegible]

Re-Classification

The results of the two histological examinations (see p 9) [illegible] ment and only a few malignant tumours that had underg[illegible] gave rise to discussion and to some difficulty in placing in th[illegible] indicates that the types of tumour described in Chapters I[illegible] cally clearly defined and well delimited with a resulting [illegible] the possibility of making an accurate diagnosis After th[illegible] re classified the whole material according to the principles [illegible] XIV

Following re-classification the parotid tumours in the [illegible] the material were distributed as shown in Table 3

A comparison can be made between the incidence of th[illegible] before (Table 1) and after re-classification (Table 3) It [illegible] decrease in the mixed tumour group is proportionate [illegible] mucoepidermoid carcinoma adenoid cystic carcinoma [illegible]

Table 3 Distribution of the tumours after re classification

Diagnosis	No	%
Mixed tumour	569	70 9
Papillary cystadenolymphoma	41	5 1
Oncocytoma	4	0 5
Misc benign tumours	67	8 4
Mucoepidermoid carcinoma	34	4 2
Adenoid cystic carcinoma	19	2 4
Acinic cell carcinoma	36	4 5
Mucus producing adenopapillary carcinoma	12	1 5
Trabecular adenocarcinoma	5	0 6
Solid anaplastic adenocarcinoma	9	1 1
Misc malignant tumours	6	0 7
Total	802	100 0

groups This suggests that these types of tumour were primarily diagnosed chiefly as mixed tumours By separation of these types from the diffuse mixed tumour group, this has become more distinctly defined histologically than before

After re classification, each type of tumour is clearly defined histologically, according to the principles described in Chapters IV—XIV Consequently the grade of malignancy of the tumours can be evaluated, with greater certainty than earlier, by a study of the correlation between the histological and clinical features of the different types

CHAPTER IV

Mixed Tumours

Definition

The term mixed tumour was introduced in 1874 by Minssen, to stress that this type of tumour was of both epithelial and mesenchymal origin. This theory started to be abandoned as early as the beginning of the present century. Nowadays, it is regarded as established that the mixed tumours are of purely epithelial derivation and that they originate in fully developed salivary-gland tissue. The most difficult problem in the concept of an epithelial histogenesis has been to explain the development of the mesenchyma-like myxoid, chondroid and fibroid components from epithelial cells.

Electron microscopical studies (Oota & Takahashi 1958, Mylius 1960), as well as histochemical (Grishman 1952) and histological studies (Gricouroff 1953), have shown that the myoepithelial cells lying in intercalated and intralobular ducts between the basement membrane and the luminal epithelium play a highly important role as a site of origin of the aforementioned mesenchyma-like components. Even though these components have thus proved to be of epithelial derivation, they will — in view of their appearance — be denoted in the following as mesenchymal.

Since it is now generally accepted that the tumours in question are derived solely from the epithelium, the term mixed tumour has started to be regarded by many authors as out of date and incorrect. Several other denotations have been suggested. Examples are 'epithelial mixed tumour' (Therkelsen 1934), "complex adenoma" (Foote & Frazell 1954, Johnson & Childers 1954), "pleomorphic adenoma and adenocarcinoma" (Willis 1960), 'pleomorphic sialoadenoma" (Rauch 1959) and 'epithelioma remanie' (Redon 1960). Mixed tumour is, however, still the most common term, and will therefore be used in the present work. It need not, in fact, refer to the histogenesis, but can be considered as purely histologically descriptive.

Histological Features

Description

A mixed tumour has both epithelial and mesenchymal components (Fig. 2). If either of these main components is lacking, the tumour should not be denoted as a true mixed tumour. This is pointed out especially to stress the borderline between a true mixed tumour and the still diffuse concept of this type of tumour found in many classifications (*e.g.* Redon 1960, Willis 1960). The histological features are described in detail in a later section of this chapter and in connexion with *Figures 3—12*.

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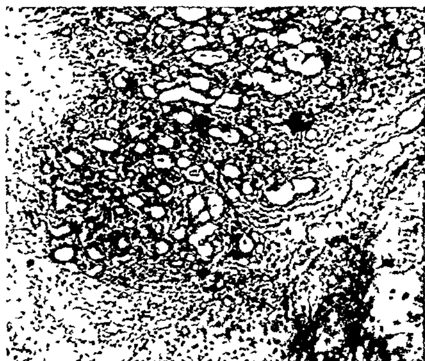


Fig. 2. Benign mixed tumour. Photomicrograph, × 50. Fibroid, myxoid, chondroid and epithelial components.

Re-classification

In the present material, a primary diagnosis of mixed tumour was made in 618 patients. My histological re-examination showed, however, that many of them did not fulfill the aforementioned criterion of a true mixed tumour, but could be referred to some other distinctly defined type of tumour described in recent years. The results of my histological study and re-classification are seen in Table 4.

Table 4. Re-classification based on histological re-examination of 618 so-called mixed tumours

Diagnosis after re-classification	No. of tumours
True mixed tumour	562
Papillary cystadenolymphoma	1
Oncocytoma	2
Neurofibroma	1
Mucoepidermoid carcinoma	5
Adenoid cystic carcinoma	14
Acinic-cell carcinoma	19
Mucus producing adenocarcinoma	7
Solid anaplastic adenocarcinoma	6
Squamous-cell carcinoma	1
Total	618

It is evident from Table 4 that only 562 of the 618 tumours primarily diagnosed as mixed tumours proved to be true mixed tumours Thus 56 tumours distributed among 9 different types, could be separated from the original diffuse collective group This implies that the remaining 562 true mixed tumours are clearly defined histologically, and characterized by a microscopical picture distinguished by a diversified mixture of epithelial and mesenchymal components

At my histological re examination of all the parotid tumours operated on in 1950—1962, I found an additional 7 true mixed tumours They had previously been listed under completely different diagnoses, *e g* mucoepidermoid carcinoma or mucus producing adenocarcinoma Thus, the total number of true mixed tumours, including the 562 separated from the diffuse mixed tumour group, amounted to 569

Grading of Malignancy

Infiltrative destructive growth of a tumour into surrounding tissue is a generally accepted histological sign of malignancy Apart from the infiltrative destructive growth, several other histological traits of a mixed tumour have been used as a basis for grading the malignancy Examples are high cellularity (Patey 1930, Ahlbom 1935), a predominance of epithelial components (McFarland 1942), cylindromatous structures (Ahlbom), incomplete encapsulation (Masson 1924) and primary multiple foci (Masson)

Different principles

At the present time, opinions are greatly at variance regarding the malignancy of the mixed tumours Many consider the entire group to be potentially malignant or so called semi malignant (*e g* Utendorfer 1955, Agner & Nielsen 1956, Rauch 1959, Schreiner 1959, Glaser 1962, Hellner 1962) Others believe the whole group to be benign (*e g* Kirklin *et al* 1951), or else malignant (Dockerty & Mayo 1942, Dargent 1952, Perzik 1957) Morehead (1962) classified the salivary-gland tumours, from the point of view of malignancy, into benign, intermediate and malignant The mixed tumours were denoted, according to their microscopical picture, as either intermediate or malignant, but never as benign

Table 5 Malignancy of mixed tumours according to Ahlbom (1935)

I *Benign*	Encapsulated solitary poorly or moderately cellular without marked cell polymorphism
II *Semi malignant*	A Encapsulated 1 Highly cellular 2 Cells markedly polymorphous 3 Basaliomatous or cylindromatous structures B Multiple foci and penetration of capsule without infiltrative growth
III *Malignant*	A Infiltrative destructive growth B Metastases

Masson and Ahlbom, among others, divided the mixed tumours into three types of malignancy, on the basis of certain histological criteria, as listed in Table 5

Grading of present material

As can be inferred from Table 4, 562 true mixed tumours remained in the present material, after separation of 56 tumours, distributed among 9 different types from the earlier diffuse group All these 562 tumours were primarily classified as mixed, and their malignancy graded according to Masson's and Ahlbom's principles (Table 5) As stated earlier, my retrospective histological study of the whole operative material disclosed an additional 7 true mixed tumours Since, however they had primarily been diagnosed as completely different types of tumour, their malignancy had not been evaluated on the same principles as in Table 5 The previous distribution by malignancy of the 562 true mixed tumours primarily diagnosed as such, is shown in Table 6

Table 6 Primary malignancy of 562 true mixed tumours according to Masson's and Ahlbom's principles

Malignancy		No	%
Benign		260	46.2
Semi malignant		282	50.2
Malignant		20	3.6
	Total	562	100.0

It is apparent from Table 6 that just over 50 per cent of the 562 true mixed tumours were primarily denoted as semi malignant, which implies great uncertainty from the clinical and therapeutical point of view

An account of my evaluation of the malignancy based on a study of the correlation between the histological and clinical features of these tumours will be given in the following sections of this chapter

CORRELATION BETWEEN HISTOLOGICAL AND CLINICAL FEATURES

The existing uncertainty about the malignancy of the mixed tumours is apparent from the variation in size of the semi malignant group in different series, i.e., from 0 to 100 per cent In most series all or an extremely large number of mixed tumours are still denoted as semi malignant Thus, in my series this applied to m[illegible] than 50 per cent in the primary evaluation of the malignancy which was mad[illegible] to Masson's and Ahlbom's principles This implies that they were denoted [illegible] malignant if they fulfilled one or more of the histological criteria

such as high cellularity, predominance of epithelial components cylindromatous structures, incomplete encapsulation and multiple foci Whereas infiltrative destructive growth is a generally accepted sign of malignancy, there is still great controversy about the prognostic value of the histological criteria of semi malignancy in mixed tumours without infiltrative growth

Consequently, the aim of the present investigation was, in the first place, to determine the effect on the clinical course of various histological criteria of semi-malignancy in mixed tumours without infiltrative destructive growth A further aim was to demonstrate the malignancy in the presence of infiltrative destructive growth For this purpose, the material was divided into two main groups *i e*, one consisting of 553 mixed tumours without infiltrative destructive growth, and one consisting of 16 mixed tumours with such growth The clinical follow up study was based on the series operated on in 1950—1957, *i e* 369 patients, 360 of them had a tumour without infiltrative destructive growth, and 9 a tumour with such growth

Mixed Tumours Without Infiltrative Destructive Growth

Tumour Components and Cellularity

Histological features

The microscopical picture of mixed tumours is characterized by a diversified mixture of epithelial and mesenchymal components The epithelial cells proliferate in masses and strands, and when there is a dominance of this component, the tumour appears highly cellular (Fig 3) The mesenchymal component usually consists of fibroid myxoid and chondroid structures

The myxoid structures consist of stellate or spindle like cells, scattered diffusely or arranged in a network in a myxoid ground substance (Fig 4) In some areas this ground substance is thickened, the cells are then detached from their network and collected in small groups (Fig 5) In view of the similarity to cartilage, these structures are denoted as chondroid Since the individual cells are pushed away from each other by the intercellular ground substance in the myxoid and chondroid components they lie more scattered than in the epithelial masses Therefore, when the mesenchymal component is dominant, the tumour has a lower cell content Exceptions are the extremely rare cases (two in my series) in which the mesenchymal component is characterized by a great abundance of cells, in the form of palisade like formations of spindle cells (Fig 6) These tumour cells resemble those in tumours of the smooth muscle and, according to *e g* Sheldon (1943) derive from the myoepithelial cells of the salivary ducts

As a rule either the epithelial or the mesenchymal component predominates sometimes to such an extent that the tumour seems to be purely epithelial or mesenchymal A purely epithelial tumour is often diagnosed as an adenoma but in the opinion of *e g* Rawson *et al* (1950), Kirklin *et al* (1951), Willis (1953) and

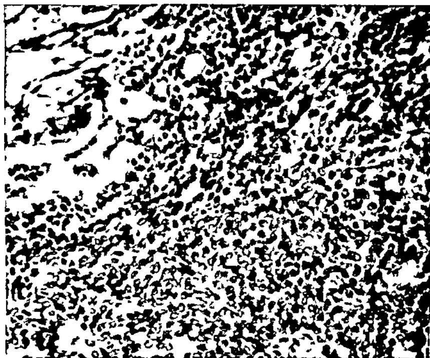


Fig 3 Benign mixed tumour Photomicrograph × 130 Highly cellular epithelial component

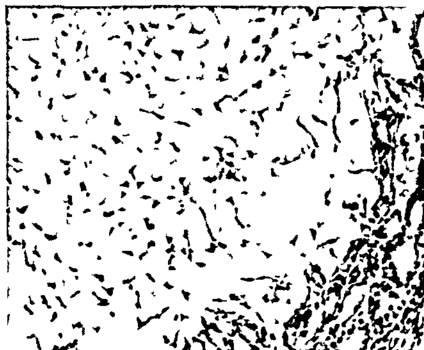


Fig 4 Benign mixed tumour Photomicrograph × 130 Myxoid component with stellate and spindle-like cells and wide intercellular spaces



Fig 5 Benign mixed tumour Photomicrograph × 130 Chondroid component with few cells collected in small groups

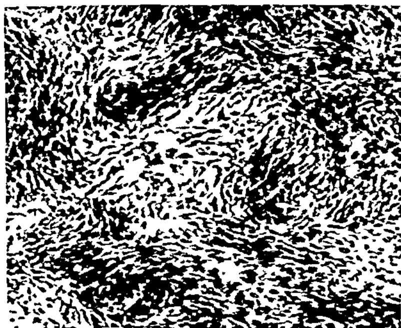


Fig 6 Benign mixed tumour Photomicrograph × 130 Fibrous component with palisade arrangement of cells

Mathis (1954), pure parotid adenomas do not occur, and such a neoplasm is actually a mixed tumour with a predominance of the epithelial component

Correlation to clinical course

To study the prognostic implication of cellularity and of the predominance of epithelial and mesenchymal components, respectively, in the mixed tumours, I divided the material into four groups, on the basis of certain histological criteria

The first group consisted of 209 mixed tumours with predominantly mesenchymal components and therefore poorly cellular, and the second group of 96 predominantly epithelial, highly cellular tumours

The third group consisted only of 2 mesenchymal highly cellular tumours, which comprised an exception to the rule that such tumours are poorly cellular The fourth group contained 53 tumours in which mesenchymal and epithelial components were present to approximately the same extent

The clinical course of the tumours in these four groups is summarized in Table 7

The results of the investigation showed that no patient in any of the four groups had died of the tumour disease No metastases were demonstrable in any case Local recurrences had occurred in 5 of the 189 followed-up patients in the 5 year survival group who had a predominantly mesenchymal, poorly cellular tumour, and in 5 of the 89 with a predominantly epithelial, highly cellular tumour No significant difference was present between these two groups with respect to the incidence of local recurrence ($\chi^2 = 1.54$) Totally 11 local recurrences were noted in the whole series 10 of them occurred after secondary operation, and only one after primary operation

It is apparent from Table 7 that the observed 5 year survival rate was 96.5

Table 7 Dominance of different tissue components and varying cellularity in mixed tumours correlation between histological and clinical features (5-year follow-up period)

Histological features	No of patients		Died of	
	Total	Followed up	Intercurrent disease	Tumour disease
Dominance of mesenchymal poorly cellular tissue	209	204	7	0
Dominance of epithelial highly cellular tissue	96	94	2	0
Dominance of mesenchymal highly cellular tissue	2	2	0	0
No definite dominance of any component	53	50	2	0
Total	360	350	11	0

[1] Alive according to Parish Register but no follow up examination made at Radiumhemmet

per cent in the group with a mesenchymal, poorly cellular tumour, and 97 8 per cent in the group with an epithelial, highly cellular tumour After correction for the deaths in intercurrent diseases, the calculated 5-year survival rate is 100 per cent in both groups All 9 deaths in these two groups were, in fact, due to an intercurrent disease and not to the tumour disease

Discussion

High cellularity was one of Ahlbom's criteria of *semi malignancy* McFarland (1942) investigated the prognostic implications of a predominance of the various components in mixed tumours of the parotid gland He divided his material into two main groups, in one of them the mesenchymal component predominated (149 tumours), and in another the epithelial component (34 tumours) He found a distinct difference in the rate of recurrence, *i e*, 38 per cent in the predominantly mesenchymal tumours, as compared to 60 per cent in the predominantly epithelial ones

Foote & Frazell (1954) studied the influence of the cellularity on the clinical course in 250 mixed tumours The follow up period was > 5 years in totally 204 cases (142 primary and 62 secondary tumours), but no definite conclusions could be drawn from the results Many authors have, however, ascribed prognostic importance to high cellularity and predominance of the epithelial component

The present investigation was based on 360 mixed tumours, of which 350 were followed up for more than 5 years It showed that high cellularity and dominance of the epithelial component were not associated with any malignancy in the form of mortality in the tumour disease or metastases Nor was there any significant difference in the incidence of local recurrence as compared to that in poorly cellular mesenchymal tumours

	5-year survival					
Metastases	Local recurrence	No follow up exam ¹	Asymptomatic	Total	Observed %	Calculated %
0	5	8	184	197	96 5	100 0
0	5	3	84	92	97 8	100 0
0	1	0	1	2	—	—
0	0	1	47	48	96 0	100 0
0	11	12	316	339		

This implies that high cellularity of a tumour or a predominance of the epithelial component cannot be used as a criterion of semi malignancy For, in the present investigation, neither the cellularity nor the predominance of various tumour elements proved to influence the grade of malignancy of the mixed tumours

Cylindromatous Structures

Histological features

In my histological re examination of 360 true mixed tumours without infiltrative destructive growth, operated on in 1950—1957 I [illegible] extent in 103

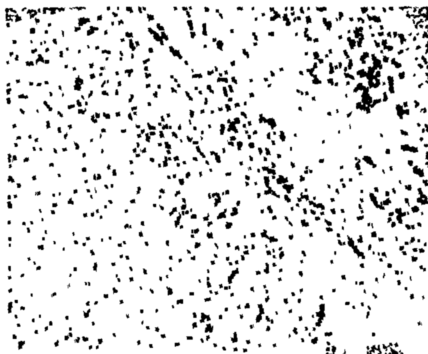


Fig 7 Be[illegible] [illegible]graph × 30 Epithelial component dominated by cylindrom[illegible]

Table 8 Mixed tumours with and without cylindromatous structures correlation between histological and clinical features (5 year follow-up period)

	No of patients		Died of	
Histological features	Total	Followed up	*Intercurrent* disease	Tumour disease
Cylindromatous structures	103	101	3	0
No cylindromatous structures	257	249	8	0
Total	360	350	11	0

[1] Alive according to Parish Register but no follow up examination made at Radiumhemmet

cases a highly characteristic arrangement of the epithelial elements Thus, the epithelial cells were relatively small, and in places formed islands and strands containing cylinders of poorly cellular, hyaline stroma These cylindromatous structures were present in tumours containing both myxoid and chondroid or other mixed tumour components in varying proportions (Fig 7) In 49 tumours, the epithelial component was dominated by these cylindromatous structures

Correlation to clinical course

The prognostic importance of cylindromatous structures in a true mixed tumour was evaluated on the basis of a clinical follow up study The material was divided into two groups, *i e*, mixed tumours with and without cylindromatous structures The results are given in Table 8

It is evident from Table 8 that none of the patients in either group died of the tumour disease *Metastases were not demonstrable in any case*

In the 5 year survival group, local recurrences occurred in 3 of the 95 followed up cases in which the tumour had cylindromatous structures, the corresponding incidence in the tumours without such structures was 8 of 232 No significant difference was present between the groups in this respect ($\chi^2 = 0\ 017$) The observed 5 year survival rate was 98 0 and 96 4 per cent, respectively, and the calculated survival rate 100 per cent in both groups

Discussion

Cylindromatous structures in a mixed tumour are regarded by many authors to be an indication of some malignancy (*e g* Ahlbom Kirklin *et al*) These structures have, however, been demonstrated in several completely different types of tumour of a varying degree of malignancy, such as adenoid cystic carcinoma (Quattlebaum *et al* 1946) mixed tumour (Therkelsen Ahlbom, Dockerty & Mayo 1942, Günnel 1956 Miehlke 1960), adamantinoma and basalioma (*e g* Naumann 1958) and hydradenoma or "turban tumour" (Boyd 1953)

Owing to the often diffuse delimitation of the mixed tumour concept, many separate types of tumour — among them adenoid cystic carcinoma — are still denoted

	5 year survival					
Metastases	Local recurrence	No follow up exam [1]	Asymptomatic	Total	Observed %	Calculated %
0	3	4	92	99	98 0	100 0
0	8	8	224	240	96 4	100 0
0	11	12	316	339		

as mixed tumours This clinically definitely malignant type of tumour differs histologically from the mixed tumours by its lack of myxoid and chondroid components, as well as by its infiltrative, typical growth, often into perineural lymph spaces

In my histological re examination of the present material, I found 19 adenoid cystic carcinomas with a typical structure Fourteen of them had previously been classified as mixed tumours Thus, "mixed tumours" with cylindromatous structures proved, in several cases, not to be true mixed tumours, but clearly malignant adenoid cystic carcinomas This earlier diffuse distinction between a true mixed tumour with cylindromatous structures and adenoid cystic carcinoma does, in all probability, explain why the former type of tumour was presumed to be malignant

In the present study, a statistical analysis was made to ascertain whether the presence of cylindromatous structures in a true mixed tumour affects the clinical course An analysis of the correlation between mixed tumours with and without cylindromatous structures, respectively, and the corresponding clinical course showed no significant difference with respect either to the 5 year survival rate or the incidence of local recurrences No signs of malignancy in the form of metastases or death in the tumour disease were found in either group

Before the histological re-examination of my material, a large number of the



Fig 8 Benign mixed tumour Apparent multiple foci due to lobulation
A Photomicrograph × 6 Tumour containing closely contiguous separate foci

mixed tumours had been classified as semi malignant on the basis of cylindromatous structures However the correlation analysis showed these cylindromatous true mixed tumours to be completely benign

It can therefore be concluded that the presence of cylindromatous structures in a true mixed tumour of the parotid gland is not associated with any increased grade of malignancy Consequently this histological criterion of semi malignancy lacks justification

Multiple Foci

Histological features

A mixed tumour may be markedly lobulated In a large number of cases apparently independent tumour foci can be demonstrated outside the actual tumour These satellite foci lie at a varying distance from the main tumour both within the normal salivary gland tissue and in surrounding tissues such as adipose tissue musculature and connective tissue A nodule that was encapsulated and apparently completely separated from the main tumour often proved on serial sectioning of the paraffin embedded specimen to be confluent with the actual tumour (Fig 8 A and B) Thus the satellite focus was often only seemingly separate and con



B Photomicrograph × 6 The same tumour after sectioning The foci are confluent

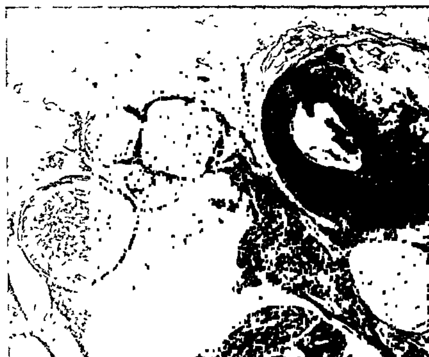


Fig 9 Benign mixed tumour Photomicrograph, × 6 Tumour growing in true independent foci

sisted of a tumour lobule which, owing to the direction of sectioning, gave the impression of being an isolated focus

Multiple foci in the vicinity of the actual tumour cannot be stated, with certainty, to be separate from it unless serial sections are made of the tissue between the two structures If, on the other hand, tumour nodules lie at a considerable distance from the main tumour, either in the salivary-gland tissue or in tissues surrounding the parotid gland, it is probably a question of independent foci (Fig 9)

Incidence of multiple foci and the influence of various factors

A study was made of the incidence of multiple foci, and of the influence of aspiration biopsy and of surgical interventions on this incidence (For details of the aspiration biopsy technique, reference is made to Mavec *et al*) The study was based on the 553 mixed tumours without infiltrative destructive growth in the original material

Table 9 shows the results of my histological re-examination of the tumours primarily stated to grow in multiple foci It also shows the incidence of aspiration biopsy and of previous operation in these cases

It is evident from Table 9 that 131 of the 553 mixed tumours (about 23 per cent were originally diagnosed as multifocal At my histological re-examination, serial sectioning was performed in doubtful cases, and 64 cases of so-called multiple foci proved to be only seemingly multiple They were, in fact, tumour lobules projecting into the salivary-gland tissue, which — owing to the direction in which

Table 9. Mixed tumours with primarily diagnosed multiple foci, and the influence of aspiration biopsy and surgical intervention on their incidence: results of histological re-examination

		No. of patients	Multiple foci: Primary diagnosis	Multiple foci: Author's diagnosis No.	Multiple foci: Author's diagnosis %
Primary tumours	No aspiration biopsy	268	45	0	0
	Aspiration biopsy	199	24	3	1.5
Secondary tumours		86	62	64	74.4
	Total	553	131	67	

the sections were cut — gave the impression of being satellite foci. Of the remaining 67 cases, in which discrete multiple foci were present with relatively great certainty, 64 were secondary cases, *i.e.*, the tumour had been operated on previously.

Multiple foci could be demonstrated with certainty in only 3 of the 467 primary cases. Aspiration biopsy had, however, been performed earlier in all 3 cases. Multiple foci were not found in any of the 268 primary tumours unassociated with aspiration biopsy.

Correlation to clinical course

Thus, true multiple foci occurred — apart from in three primary tumours with previous aspiration biopsy — only in secondary cases, *i.e.*, in tumours operated on before (Table 9). To study the correlation between multiple mixed-tumour foci and the clinical course for at least 5 years after operation, all 34 cases with multiple foci operated on in 1950—1957 were followed up. All of them were secondary cases. During this period, operation had been performed on another 15 secondary cases, in which no multiple foci were demonstrable.

The clinical course in these two groups can be inferred from Table 10.

This clinical follow-up study showed that multiple foci in a secondary tumour were not associated with metastases or death in the tumour disease in any case. No significant difference was present between the incidence of local recurrence in secondary tumours with multiple foci (8 of 32 followed up patients in the 5-year survival group) and without them (2 of 15), respectively ($\chi^2 = 0.83$).

Discussion

Many authors regard multiple foci in a mixed tumour to be a sign of some malignancy (*e.g.* Ahlbom, Masson). Opinions are, however, greatly at variance regarding whether multiple mixed tumours do, in fact, occur primarily. Ewing (1940), McFarland (1943), Willis (1953, 1960), Mathis (1954), Delarue (1956) and Redon (1957) among others expressed the view that a mixed tumour derives from a number of tumour anlagen, diffusely and irregularly scattered in the glandular parenchyma.

Table 10 Secondary mixed tumours with and without multiple foci correlation between histological and clinical features (5-year follow-up period)

Histological features	No of patients		Died of	
	Total	Followed up	Intercurrent disease	Tumour disease
Multiple foci	34	34	1[1]	0
No multiple foci	15	15	0	0
Total	49	49	1[1]	0

[1] Alive according to Parish Register but no follow up examination made at Radiumhemmet

Foote & Frazell as well as Patey & Thackray (1958), Rauch (1959), Beahrs *et al* (1960) and Grage *et al* (1961 b), among others pointed out on the contrary that multiple nodules only occur exceptionally in a primary mixed tumour According to *e g* Foote & Frazell as well as Grage *et al* and Patey & Thackray, multiple nodules are almost invariably present in a secondary mixed tumour

Günnel (1961 a) stated that to determine definitely whether multiple foci occur primarily the specimen must be serially sectioned from the satellite foci towards the main tumour In his series he demonstrated that many of the so called satellite nodules were actually confluent with the tumour Gunnel emphasized that the authors who held the view that primary mixed tumours may be an aggregate of nodules had not performed such serial sectioning so that their conclusions were not authenticated The object of Gunnel's investigation was to provide evidence of the presumption made by Foote & Frazell and Beahrs *et al*, among others that multiple foci do not occur primarily The investigation was based on a small series (71 cases and as far as I am aware, no similar study has been reported

To ascertain whether multiple nodules do in fact occur primarily I made a histological re-examination of the 553 mixed tumours in the present series When there was any doubt regarding the authenticity of the multiple nodules serial sectioning was done I then found that a large number (about 50 per cent) of the so-called multiple foci were actually severed lobules which owing to the direction in which the sections were cut gave the impression of being independent foci After exclusion of all these cases it was found that genuine multiple nodules occurred in a high incidence in secondary tumours but not at all in primary tumours unless aspiration biopsy had been done prior to operation

The investigation thus showed that a primary tumour does not consist of multiple nodules but that these appear only after various manipulations of it — *in a high incidence after previous operation* (in my series in 64 of 86 cases) *and in an extremely low incidence after aspiration biopsy (in 3 of my 199 cases) According to e g* Janes 1943 Martin (1952 *and* Agner & Nielsen *as well as* Miehlke and Glaser *the high incidence of multiple foci in recurrent tumours is to be ascribed* to the fact that owing to deficient radicality of operation small tumour fragments are left in the salivary gland tissue as well as in surrounding tissues Byars *et al*

	5 year survival					
Metastases	Local recurrence	No follow up exam [1]	Asymptomatic	Total	Observed %	Calculated %
0	8	1	24	33	97 1	100 0
0	2	0	13	15	100 0	100 0
0	10	1	37	48		

(1957), Boswell (1959), Nickol (1955), Ackerman & del Regato (1962) and Becker (1963) have stressed the risk of spreading of tumour fragments in connexion with aspiration biopsy, with a resulting risk of recurrence of a mixed tumour

In my large series of mixed tumours it could be shown that multiple foci do not, as a rule, occur in a primary tumour, whereas they are present in a high incidence in secondary tumours (71·4 per cent) In no case was a secondary tumour with multiple nodules responsible for metastases or death

Consequently, the high incidence of recurrence in secondary tumours with multiple foci must be attributed to incomplete removal of the primary tumour, and not to its malignancy This implies that the presence of multiple foci in a mixed tumour is not a suitable criterion of semi malignancy

Encapsulation

Histological features

In mixed tumours the relation between tumour capsule and surrounding salivary gland tissue varies greatly, as do the other histological structures The tumour is sometimes completely invested by a capsule of varying thickness The tumour tissue may grow into the capsule, so that it is split up, or differs greatly in thickness with the result that the tumour is more or less lobulated In some cases the tumour tissue may completely penetrate the capsule (Fig 10), so that it is contiguous to e g normal salivary gland or adipose tissue without infiltrative destructive growth into these tissues

A capsule may also be lacking to a greater or lesser extent, so that the tumour tissue is directly adjacent to the salivary-gland tissue, although — despite the absence of a capsule — the tumour is relatively clearly delimited (Fig 11 A—D)

Correlation to clinical course

The material for this part of the investigation consisted of the 360 mixed tumours without infiltrative destructive growth into surrounding tissues, and operated on in 1950– 1957 By means of a 5 year follow up study, it was possible to evaluate

Table 11 Mixed tumours with penetration of the capsule or local incomplete encapsulation correlation between histological and clinical features (5-year follow up period)

No of patients		Died of			5-year survival					
Total	Followed up	Intercurrent disease	Tumour disease	Metastases	Local recurrence	No follow up exam [1]	Asymptomatic	Total	Observed %	Calculated %
46	46	1	0	0	0	1	44	45	97 8	100 0

[1] Alive according to Parish Register but no follow up examination made at Radiumhemmet.

the prognostic importance of penetration of the capsule by the tumour, and of a varying degree of incomplete encapsulation The results are given in Table 11

Penetration of the capsule or deficient encapsulation could be demonstrated in altogether 46 cases This by no means implies that the rest of the 360 mixed tumours were clearly encapsulated In 83 cases, tumour infiltration without penetration of the capsule was demonstrable The capsular structures were, actually, extremely difficult to study in the whole external aspect of the tumour In doubtful cases I cut new sections from the paraffin embedded tumour Despite this there was often great difficulty in judging the relation between the tumour tissue and that of the capsule and the surrounding salivary-gland tissue This was due either to artefacts in preparation of the tumour for microscopical examination or to lack of radicality in surgical excision so that too little marginal tissue was included

Table 11 shows that penetration of the capsule or incomplete encapsulation was observed in 46 cases Their evaluation was based on the specimens in which these conditions could be examined with certainty, in view of a sufficient amount of salivary-gland tissue It is possible that the material contained additional cases with these capsular defects although they could not be identified because of the afore mentioned difficulties

This implies that no clinical follow up comparison could be made between encapsulated tumours and those with incomplete encapsulation On the other hand the prognostic importance of such capsular defects as those illustrated in Figures 10 and 11 can be inferred from Table 11 None of the 46 patients registered in Table 11 died of the tumour disease nor did a local recurrence or metastases occur in any of them

Discussion

Owing to expansion of the tumour the salivary-gland tissue surrounding it is compressed into the fibrous stroma which forms the "capsule (Patey & Thackray Perzik 1957 1958 Grage et al 1961 b) This explains the often deficient encapsulation of extremely small tumours (Grage et al Gunnel 1961 b) According to Boswell (1959 mixed tumours were as a rule earlier regarded as encapsulated so that excision without inclusion of any surrounding marginal salivary gland tissue was the routine procedure

Agner & Nielsen and Becker (1958), among others, have stated that this surgical method is associated with a great risk of local recurrence, in view of the lobulation of mixed tumours, and of the existence of defects in the capsule, with excrescences on the external aspect of the tumour Excrescences projecting into surrounding salivary gland tissue have been described by *e g* Foote & Frazell, as well as Utendorfer (1955, 1956), Gunnel (1961 b) and Becker (1958) According to Gunnel and Utendorfer, such excrescences occur in about 1/3 of all mixed tumours

Buxton *et al* (1953) and Perzik (1957), as well as Beahrs *et al* and Grage *et al* (1961 b), have shown that more radical removal of primary mixed tumours (parotidectomy) has reduced the incidence of recurrence from > 10 to < 1 per cent The previously high incidence of recurrence must therefore be ascribed to the surgical technique, which did not include removal of sufficient marginal salivary gland tissue, so that small tumour excrescences were left in this tissue Consequently, the high incidence was not due to any increased grade of malignancy in mixed tumours with capsular structures of the kind described Incomplete encapsulation of a varying extent, with tumour tissue contiguous to salivary gland tissue, has been reported by Patey & Thackray, as well as by Bishop (1960), Willis (1960) and Gunnel (1961 b), among others Growth into the capsule and penetration of it has also been demonstrated by *e g* Gunnel (1961 b)

The literature thus contains several thorough descriptions of various histological details of the capsular structures, but no clinical follow up study of tumours associated with them has been found Great prognostic value has been attributed to these structures by different authors (*e g* Ahlbom, Masson) Despite this, I have

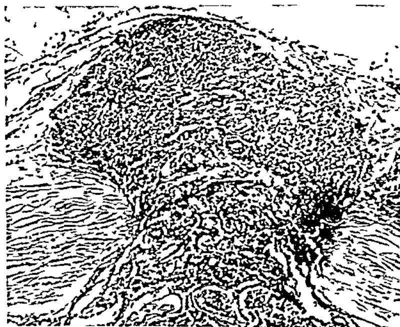
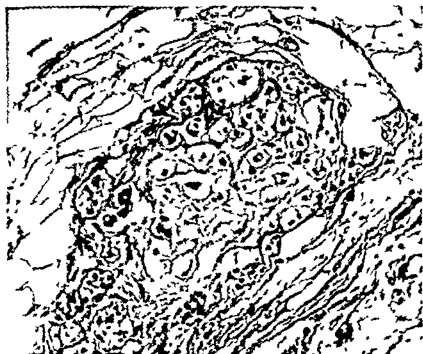


Fig 1 Benign mixed tumour Photomicrograph × 50 Tumour tissue penetrating the capsule and protruding beyond it.



Fig 11 Benign mixed tumour More or less incomplete encapsulation.

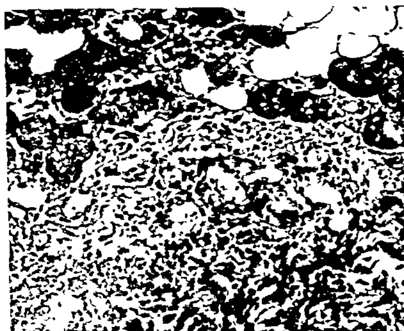
A Photomicrograph × 50 Knob shaped protrusion of the tumour into the surrounding adipose tissue



B Phc r r graph × 130 The same tumour at higher magnification Tumour cells in direct contact w i l pose cells



C Photomicrograph × 50 Tumour tissue, without capsule, adjacent to fat involuted salivary gland tissue

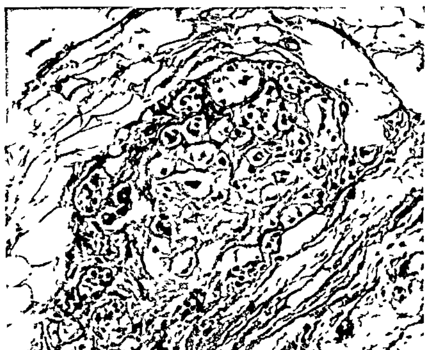


D Phot micrograph × 130 The same tumour at higher magnification, showing the intimate cont etween tumour tissue and salivary gland tissue



Fig 11 Benign mixed tumour More or less incomplete encapsulation

A Photomicrograph × 50 Knob shaped protrusion of the tumour into the surrounding adipose tissue



B Photomicrograph × 130 The same tumour at higher magnification Tumour cells in direct contact with adipose cells

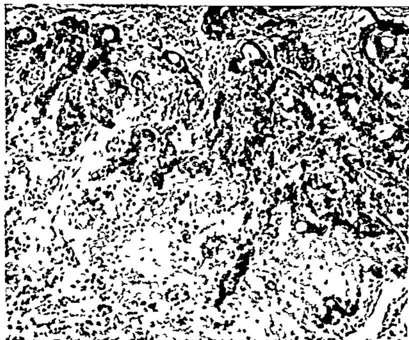


Fig 12 Malignant mixed tumours

A Photomicrograph × 50 Tumour with fibroid, myxoid, chondroid and epithelial components The epithelial component shows marked cellular polymorphism



B Photomicrograph × 130 Tumour with tentacular invasive growth of the solid epithelial component

been *unable to trace any report with conclusive evidence that incomplete encapsulation* without infiltrative destructive growth is actually a sign of malignancy.

Masson based his grading of the malignancy of mixed parotid tumours precisely on the conditions of encapsulation. He divided these tumours into three groups *i.e.* benign, semi-malignant and malignant. The benign group consisted of encapsulated tumours, in which the tumour tissue might penetrate into the capsule, but not beyond it. Once the capsule had been penetrated by tumour tissue, or some part of the tumour was not encapsulated, it was denoted as semi-malignant. The tumour was not regarded as malignant until there was infiltrative destructive growth into *surrounding tissues*.

This classification was adopted and elaborated by Ahlbom. After publication of his monograph in 1935 it was accepted internationally and is still used in much of the modern literature.

The present results show that penetration of the capsule by a mixed tumour, or its incomplete encapsulation, is not associated in any way with signs of increased malignancy. Consequently, it is not justified to base the concept of semi-malignancy on these features.

Mixed Tumours with Infiltrative Destructive Growth

Histological features

A true mixed tumour may exhibit infiltrative destructive growth into adjacent salivary gland tissue but also into adipose and muscular tissue, as well as into lymph and blood vessels.

To fulfill the histological criteria of a mixed tumour, the tumour must contain both epithelial and mesenchymal components (Fig. 12 A). In these tumours with *infiltrative growth the epithelial component is markedly polymorphous* and carcinomatoid and often dominates the infiltrative part of the tumour (Fig. 12 B). The mesenchymal component, on the other hand, is generally fibroid and less frequently myxoid or chondroid.

In the present material tumours with a strongly polymorphous epithelial cell pattern have been classified as malignant mixed tumours only when mesenchymal elements (fibroid, myxoid or chondroid) were also demonstrable. However, it was hard to judge both the appearance of the cells and the extent of the various tumour *components in view of regressive irradiation changes* such as cell atypia and hyalinization (8 of 9 cases irradiated preoperatively). Actually it was difficult in most of these exceedingly rare mixed tumours with infiltrative growth to evaluate the histological structures motivating the diagnosis of mixed tumour. However, in the *present 9 cases both epithelial and mesenchymal components were demonstrable* which established the diagnosis.

Correlation to clinical course

Infiltrative destructive growth into surrounding tissues could be demonstrated in only 9 of the 369 true mixed tumours with a follow-up period of $>$ 5 years, 4 of

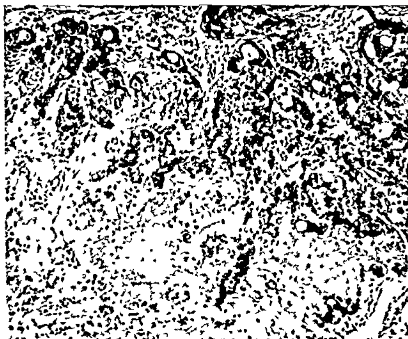


Fig 12 Malignant mixed tumours

A Photomicrograph × 50 Tumour with fibroid myxoid chondroid and epithelial components The epithelial component shows marked cellular polymorphism



B Photomicrograph × 130 Tumour with tentacular invasive growth of the solid epithelial component

Table 12 Mixed tumours with and without infiltrative destructive growth correlation between histological and clinical features (5-year follow-up period)

Histological features	No of patients		Died of	
	Total	Followed up	Intercurrent disease	Tumour disease
Infiltrative destructive growth	9	9	2	4
No infiltrative destructive growth	360	350	11	0
Total	369	359	13	4

¹ Alive according to Parish Register but no follow up examination made at Radiumhemmet

the 9 were primary cases The prognostic implication of such growth is evident from Table 12, which shows the clinical course in mixed tumours with and without infiltrative destructive growth

It can be inferred from Table 12 that the tumour was responsible for death in only 4 of the 359 followed up cases and that metastases were present in 3 of the 4 All these malignant tumours belonged to the group of mixed tumours with infiltrative destructive growth whereas the group of tumours without infiltrative destructive growth contained no case of metastases or death in the tumour disease The observed 5 year survival rate is 33 and 97 per cent respectively and the calculated 5 year survival rate after correction for the mortality in intercurrent diseases is 56 and *100 per cent in the respective groups The corresponding figures for the incidence of* recurrence are 56 and 3 per cent

These results show, without any shadow of doubt a clear cut difference between mixed tumours with and without infiltrative destructive growth as far as malignancy is concerned *i e* the former are definitely malignant and the latter are benign

The question then arises whether any further grading of the malignancy of mixed tumours with infiltrative destructive growth can be made on the basis of the extent of this growth

My histological re examination disclosed diffuse invasion (6 cases) as well as *relatively well delimited tumours with localized invasion of blood and lymph vessels* (2 cases) and tentacular invasion of the salivary gland tissue (1 case) Is this difference in degree of infiltrative growth of any prognostic value?

To investigate this question, the 9 tumours with infiltrative destructive growth were divided into two groups *i e* one with diffuse invasion (6 cases) and the other with localized invasion (3 cases) The results of the clinical follow up study showed a distinct difference between the groups with respect to the incidence of recurrence and metastasis as well as mortality in the tumour disease No definite conclusions can be drawn regarding this difference in view of the small number of *observations It is however* clear that *mixed tumours with diffuse infiltrative* destructive growth have a particularly poor prognosis with a calculated 5 year survival rate of approximately 33 per cent Four of the 6 patients died of the tumour disease in 3 of them metastases to regional lymph nodes were demonstrable In 2 of these 3 there were in addition distant metastases to the lungs brain and

Metastases	Local recurrence (total)	5 year survival					
		Local recurrence	No follow up exam [1]	Asympto-matic	Total	Observed %	Calculated %
3	5	1	0	2	3	33 3	55 5
0	11	11	12	316	339	96 8	100 0
3	16	12	12	318	342	95 3	98 9

mediastinum In the fourth patient, whose death was caused by invasion of the brain after destruction of the base of the skull no metastases were demonstrable The group of tumours with diffuse, infiltrative destructive growth contained an additional two patients one of whom died of an intercurrent disease 5 years after primary operation The autopsy report made no mention of the tumour conditions Although the other patient survived for > 5 years (the only case in this group), operation for a recurrence of the tumour was done after 3 years and he died of an intercurrent disease barely 6 years after the primary operation

In the group of mixed tumours with localized infiltrative growth one patient died of an intercurrent disease 5 years after operation whereas the other two were alive and asymptomatic after > 5 years

Discussion

Infiltrative destructive growth of a tumour into surrounding tissue is a generally accepted criterion of malignancy Masson denoted those mixed tumours which invaded surrounding organs without well defined margins as mixed tumour carcinomas Ahlbom on the other hand called mixed tumours with infiltrative destructive growth malignant mixed tumours These tumours are rare, and they occur in 2—10 per cent of all cases (*e g* Rawson *et al* Frazell Bruzelius *et al* Beahrs *et al* Ackerman & del Regato) In my original material consisting of 369 true mixed tumours histological re-examination disclosed 16 with infiltrative destructive growth *i e* 2 8 per cent

The clinical follow up examination showed a definite prognostic difference between tumours without infiltrative destructive growth (360 cases) and those with such growth (9 cases)

Thus no metastasis or death in the tumour disease was demonstrable in any case in the former group whereas a high incidence of both was found in the latter group (Table 12 It might be possible to grade the malignancy more exactly on the basis of the extent of the infiltrative destructive growth A larger material is however required before any definite conclusions can be drawn

The present investigation shows that true mixed tumours may exhibit infiltrative destructive growth into surrounding tissues although this occurs in only about 2 per cent of them Moreover, this growth pattern is a sign of malignancy

Symptomatology

In the series followed up for > 5 years, local pain was recorded in 13 of 360 patients with a benign mixed tumour The pain was not particularly severe, but generally consisted of slight dull pain, a feeling of pressure or a pricking sensation Exceptions were a few cases in which the patient complained of violent, radiating pain in the tumour region There was no record of pain in any of the 9 patients with a malignant mixed tumour

All 13 patients with pain in the region of the tumour survived and were asymptomatic for > 5 years after operation

As far as the whole operative material is concerned — 553 mixed tumours without infiltrative destructive growth and 16 with such growth — 24 patients in the former group had a history of pain, but none of those in the latter group

In the material followed up for > 5 years, spontaneous paralysis of the facial nerve occurred in 1 of the 360 patients with a benign tumour, and in 2 of the 9 with a malignant tumour The patient in the former group was pregnant, the paralysis had its onset two days before parturition, and regressed comparatively soon after it At operation 4 months after parturition, there was, however, still slight functional impairment, but no involvement of the nerve by the tumour was demonstrable The two patients with a malignant mixed tumour and persistent spontaneous paralysis of the facial nerve died 1 and 4 years, respectively, after the onset of paralysis

Discussion

Opinions are at variance regarding the conclusions that can be drawn about the grade of malignancy from the occurrence of pain Thus, Frazell and Ackerman & del Regato (1962), among others, have expressed the view that pain is a criterion of malignancy Diamant (1956) stated that mixed tumours in general — i e, even the malignant ones — are seldom responsible for pain However, Kirklin *et al* reported pain in 5 6 per cent of benign mixed tumours, and Beahrs *et al* in 4 per cent This incidence is in good agreement with that in the present series (about 4 per cent) The fact that there was no history of pain in any of the present cases of malignant mixed tumour may have been due to this group being so small The investigation did however, show that no reliable conclusions about the malignancy of mixed tumours can be based on the symptom of pain

According to Kirklin *et al* and Gunnel (1961 a), among others, a benign mixed tumour of the parotid gland never involves the facial nerve This is borne out by the present investigation in which only one of 360 benign mixed tumours was associated with spontaneous but transient paralysis of the facial nerve Moreover, in this case the paralysis had in all probability no connexion with the parotid tumour but was presumably to be ascribed to pregnancy Spontaneous paralysis of the facial nerve during the last trimester of pregnancy has, in fact, been reported by Miehlke (1960)

Kirklin *et al* and Frizell, as well as Rauch and Beahrs *et al*, among others have stated that spontaneous paralysis of the facial nerve appearing in association with a mixed tumour is a distinct sign of malignancy The present investigation supports this view but shows, in addition, that *persistent spontaneous paralysis of the facial nerve is an exceedingly severe prognostic sign*

Summary

The histological definition of mixed tumours of the parotid gland has become increasingly distinct in recent years Despite this the concept of malignancy in this type of tumour has remained extremely unclear

Such features as high cellularity and cylindromatous structures incomplete encapsulation and penetration of the capsule, as well as multiple foci, have become successively *accepted as signs of some malignancy of the mixed tumours* The variation in the histological picture and the comparative rarity of these tumours have hitherto hampered any reliable investigation of the influence of the aforementioned factors on the clinical course This explains why the term semi malignancy, introduced by Masson, is still so widely used Thus in most of the current classifications, the group of mixed tumours is denoted either as entirely semi malignant (*e g* Rauch 1959, Glaser 1962, Hellner 1962), or as partly semi malignant (*e g* Edvall 1954, Diamant 1956 Zettergren 1956, Mylius 1960, Morehead 1962)

Before re-classification of the present material, > 50 per cent of the mixed tumours were denoted as semi malignant, in view of the presence of one or more of the previously mentioned histological criteria

The final investigation — based on a careful follow up study in a series of mixed tumours — shows that the histological criteria of semi malignancy are not associated with a higher incidence of recurrence than in the presence of definitely benign structures Nor are they responsible for metastases or death in the tumour disease Consequently, the concept of semi malignancy seems to lack any clinical justification This must have considerable practical consequences since the so-called semi malignant group is an exceedingly large one Classification of a tumour as semi malignant has as a rule implied that the patient must for his entire life undergo regular check ups once twice or even four times a year

The present results indicate, for instance, that extensive follow up examinations are unnecessary in a large number of parotid tumours (the so called semi malignant mixed tumours) A mixed tumour requires re examination at close intervals only in the rare cases in which it exhibits infiltrative, destructive growth into surrounding tissue

In this material about 70 per cent of all the tumours of the parotid gland belong to the mixed tumour group In view of the lack of justification of the term semi malignancy it can be divided into two distinctly separated groups, i e, a group of benign tumours containing about 98 per cent, and a group of malignant tumours containing the remaining 2 per cent

excretory duct, and the other two as a benign mixed tumour and adenoid cystic carcinoma respectively The latter diagnosis is explained to some extent by the fact that the patient had directly beside the papillary cystadenolymphoma a mixed parotid tumour with cylindromatous structures

Discussion

Papillary cystadenolymphoma was one of the first types of parotid tumour to be recognized (Albrecht & Arzt 1910), and its histological features are highly characteristic This is probably why practically all the 41 tumours in the present material were primarily diagnosed as such

In contrast to benign mixed tumours papillary cystadenolymphoma — which is generally accepted to be a benign type — may occur primarily in multiple foci This is explained by its histogenesis Albrecht & Arzt advanced the theory that this type of tumour develops from heterotopic fragments of salivary gland ducts in the lymph nodes around the parotid gland In studies of both foetal and normal salivary gland tissue remains of this tissue have been demonstrated in intraglandular lymph nodes in the parotid gland as well (*e g* Thompson & Bryant Seifert & Geiler 1956)

Several lymph nodes are present in the parotid gland both in the parenchyma and outside it Shaw & Friedmann (1959) and Morehead (1962) have stated that this explains the higher incidence of multiple and even bilateral papillary cystadenolymphomas as compared to that in other benign tumours of the parotid gland According to Rauch (1959) the neoplastic proliferation of the heterotopic salivary gland fragments in the lymph nodes is elicited by postfoetal disturbing mechanisms of various kinds such as dilatation produced by a calculus or inflammation In the present series I was however unable to detect any case of bilateral papillary cystadenolymphoma Foote & Frazell as well as Shaw & Friedmann found bilateral tumours in 5—12 per cent of their cases

Correlation Between Histological and Clinical Features

Results

The correlation between the histological features characteristic of papillary cystadenolymphoma and the clinical course was investigated in 18 patients who underwent a primary operation in 1950—1957 No secondary tumour was operated on during this period The results of the clinical follow up study are given in Table 14

Altogether 15 of the 18 patients were followed up for > 5 years None of them died of the tumour disease nor were metastases demonstrable in any case A local recurrence occurred in one patient but after removal of the tumour he survived and was asymptomatic for > 5 years After correction for the mortality in intercurrent diseases (2 patients) the calculated 5 year survival rate is 100 per cent

Pain had been present before operation in 2 of the 15 cases followed up for > 5 years Both patients survived and were free from symptoms after operation Spontan[illegible] [illegible]lysis of the facial nerve was not demonstrable in any of the cases

Table 14 Papillary cystadenolymphoma correlation between histological and clinical features (5-year follow-up period)

No of patients		Died of			5 year survival				
Total	Followed up	Intercurrent disease	Tumour disease	Metastases	Local recurrence	Asymptomatic	Total	Observed %	Calculated %
18	15	2	0	0	1	12	13	86.6	100.0

In the whole operative series, comprising 41 patients with papillary cystadenolymphoma, there was a history of local preoperative pain in 5 cases, but no instance of spontaneous paralysis of the facial nerve.

Discussion

In the present series, papillary cystadenolymphoma proved to be a completely benign type of tumour, which was not responsible for metastases or death in any case. This is the generally accepted view, although Rawson *et al.* (1950) and Buxton *et al.* (1953) have reported isolated cases of malignant papillary cystadenolymphoma. It is, however, probable that an incorrect diagnosis was made in these cases. According to Glaser (1962), this applies to the case described by Buxton *et al.*, in which a papillary cystadenolymphoma was transformed into a mucoepidermoid carcinoma.

As far as the incidence of recurrence is concerned, contradictory data are found in the literature. Thus, Rauch (1959) stated that this type of tumour does not recur, whereas Foote & Frazell reported the incidence of recurrence to be 12.2 per cent after primary operation of papillary cystadenolymphoma, as compared to 4.4 per cent after primary operation of benign mixed tumours. In my material, the corresponding figures are 6.6 per cent (1 of 15) and 0.3 per cent (1 of 312).

Glaser expressed the opinion that the higher incidence of recurrence in papillary cystadenolymphoma is due to the fact that multiple foci occur to any great extent only in this type of tumour. Consequently, according to Morehead (1962), it is not a question of a genuine recurrence, but of independent neoplasms which develop at different times in the heterotopic salivary gland tissue present in various lymph nodes in the parotid gland.

In my material there was a history of local pain in about 12 per cent of the cases, *i.e.*, a higher incidence than in any other type of tumour of the parotid gland including the malignant ones. This preoperative pain was not associated with any increased malignancy.

It is difficult to explain this incidence of pain in association with a benign tumour. A possibility is that the sometimes extremely rapid growth of the tumour, owing to secretion of mucus in the cystic cavities, produces a sensation of pressure or pain. The incidence of pain in my series is remarkable in comparison to the reports of other authors. Thus Mathis (1954), Rauch (1959) and Macksood *et al.* (1960)

among others stated that pain does not occur in papillary cystadenolymphoma Glaser however, found that occasional tumours of this type gave rise to pain

The tumour does not involve the nerve fibres directly This is borne out in the present series by the fact that spontaneous paralysis of the facial nerve did not appear in any case

Summary

Papillary cystadenolymphoma is a type of tumour of the parotid gland that has been recognized for many years In the present material it is found to be easily diagnosed by histological examination The tumour has highly characteristic features and is benign despite the relatively common occurrence of local pain in this series The tumour is often multiple which explains the high incidence of recurrence after primary operation as compared to that in other types of benign parotid tumours

CHAPTER VI

Oncocytoma

Definition

An oncocytoma is an exceedingly rare type of tumour, which arises from characteristic cells normally present in the salivary glands, and termed oncocytes by Hamperl (1931), among others In normal parotid tissue oncocytes never occur before 20 years of age and seldom before 50 years (Batsakis & Martz 1966) but are always present after 70 years (Hamperl) Skorpil (1940 b) has expressed the view that the oncocytes comprise an irreversible type of transformed glandular epithelium

It has been questioned by Batsakis & Martz, for instance, whether an oncocytoma is actually, a neoplasm or merely oncocytic hyperplasia, in view of the great resemblance of the normally occurring oncocytes to the tumour cells The most common synonyms of oncocytoma are "oxyphilic granular cell adenoma" (Meza-Chavez 1949), "oxyphil cell adenoma (Foote & Frazell 1954) and "azidophiles adenom" (Rauch 1959)

Histological Features

Description

The cells of the oncocytoma are homogeneous They are polygonal and relatively large, and their outlines are distinct The cells, which are eosinophilic, are granulated and have a small, dark nucleus lying in the periphery They are arranged in clumps or cords in a sparsely vascularized stroma The typical histological structure of the oncocytoma is shown in Fig 14, A and B

Re classification

At my histological re examination of the whole material, I found a tumour consisting exclusively of oncocytes in 4 patients (0 5 per cent) Three of them were primary cases The remaining patient had been operated on for a benign mixed tumour of the parotid gland 8 years later he had a recurrence', which proved to be an entirely different type of tumour i e an oncocytoma In all four cases, the tumour had been diagnosed primarily as an oncocytoma

In addition oncocytic structures were present in two cases diagnosed as mixed tumours In both cases the microscopical picture was, however, dominated by the structures typical of a mixed tumour (Fig 15)

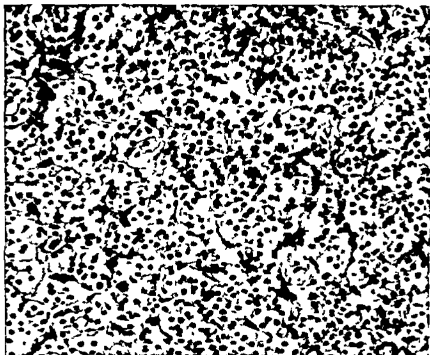
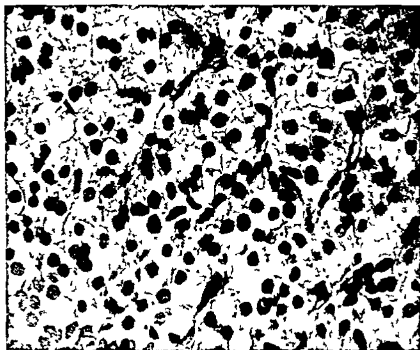


Fig 14 Oncocytoma
A Photomicrograph × 130 Homogeneous cellulai structure



B Photomi rogr ph × 300 Typ cal oncocytes with large cytoplasm and small dark nucleus

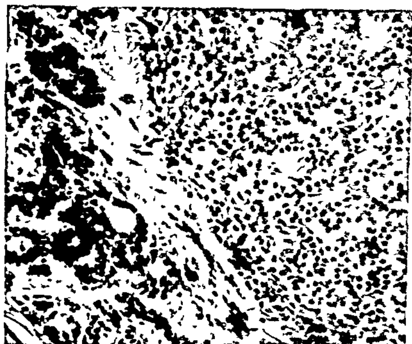


Fig 15 Benign mixed tumour Photomicrograph × 130 Area also containing oncocytic structures

Discussion

According to Hamperl (1962), the term oncocytoma should be used only to designate a tumour that is composed solely or mainly of oncocytes Consequently, only four tumours in the present material can be classified as oncocytomas, whereas the two in which oncocytic structures were present in addition to mixed tumour components must be denoted as mixed tumours

The presence of oncocytic structures in mixed tumours has been reported earlier by Christopherson (1949) and Rawson *et al* (1950) and in papillary cystadenolymphomas by Glaser (1962) Hamperl (1962) stated that oncocytoma like structures *in other types of tumour are due to the oncocytes increasing in number in the* already differentiated foreign type of tumour and thus forming foci of these cells Foote & Frazell on the contrary expressed the opinion that the oncocytes in the existing oncocytoma retain their ability to differentiate into other types of tumour which would explain the simultaneous occurrence of oncocytic structures and myxoid and chondroid components

The presence of oncocytic structures in other types of tumour has led to some hesitation about whether the oncocytoma should be separated from other types of parotid tumour However Ackerman 1943) and Foote & Frazell as well as Schafer *et al* (1956 and Glaser among others regard the oncocytoma as a morphologically clearly defined type Its histological features are highly characteristic so that the tumour is easily diagnosed Thus all four cases in my material were primarily diagnosed as oncocytomas

Correlation Between Histological and Clinical Features

The oncocytoma is an extremely rare type of salivary gland tumour, and no definite conclusions can be drawn from the total 44 cases which Hamperl (1962) was able to trace in the literature One of the four patients with a pure oncocytoma in my material was followed up for $>$ 5 years, and was then alive and asymptomatic In no case did the tumour cause pain or spontaneous paralysis of the facial nerve, which agrees with the observations of Schafer *et al* and Rauch

Although recurrences are believed to be uncommon (Glaser), no exact data are available in view of the rarity of the tumour Oncocytoma is generally regarded as a completely benign tumour (*e g* Foote & Frazell, Schafer *et al*, Beahrs *et al* 1960, Batsakis & Martz) Bauer & Bauer (1953) have, however, reported a case of malignant oncocytoma of the parotid gland with metastases

Summary

In the present investigation oncocytoma is found to be a histologically easily diagnosed tumour of the parotid gland which is extremely rare (an incidence of 0 5 per cent in this series) No signs of clinical malignancy are demonstrable Oncocytic structures are also identified in two mixed tumours It is pointed out that there is some doubt regarding whether oncocytoma is an independent type of tumour, *i e*, whether it is a genuine neoplasm or merely oncocytic hyperplasia

CHAPTER VII

Miscellaneous Types of Benign Tumours and Pseudotumours

In my histological re-examination of the present material I found several benign types of tumour that do not arise in the actual salivary-gland parenchyma, as well as so-called pseudotumours, i.e., localized swellings of varying origin such as inflammation, hyperplasia and cyst formation. Since most of these tumour types and pseudotumours are well known histologically from their occurrence at other sites, only a brief account of them will be given. Benign lymphoepithelial lesion will be described in somewhat greater detail, as there is still great controversy regarding whether this is indeed a separate type of tumour.

The distribution of the benign, non-glandular tumours and pseudotumours after re-classification of the present material is shown in Table 15.

Mesenchymal Tumours

A tumour that does not derive from the actual salivary gland parenchyma, but from the interstitial tissues of the parotid gland, is denoted as a mesenchymal tumour. In the present material, 12 patients had a benign mesenchymal tumour of some kind, i.e., neurinoma, neurofibroma, fibroma, lipoma, haemangioma or lymphangio-

Table 15. Benign non-glandular tumours and pseudotumours: diagnoses after re-classification

Diagnosis	No. of tumours
Neurinoma	2
Neurofibroma	5
Fibroma	2
Lipoma	1
Haemangioma	1
Lymphangioma	1
Epithelioma calcificans (Malherbe)	2
Retention cyst	15
Branchial cyst	5
Benign lymphoepithelial lesion	6
Lymph node hyperplasia	7
Lymphogranuloma	5
Chronic parotitis	15
Total	67

ma All these tumours have characteristic microscopical features and are easily identified Thus, in the present series, the primary diagnosis was not altered after the histological re-examination in any case

Epithelioma Calcificans (Malherbe)

Epithelioma calcificans or necroticans is a skin tumour that has been described by Boyd (1953), among others In two patients in my series, operation was performed on the indication of a parotid tumour, but microscopical examination disclosed the features typical of epithelioma calcificans On palpation, both tumours were as hard as cartilage and adherent to the skin Despite this, they were diagnosed as true parotid tumours, in view of their location in the skin over the parotid gland

Simple Cysts

Cyst formations without the presence of any tumour component — in contrast to papillary cystadenolymphoma or mucoepidermoid carcinoma — are denoted here as simple cysts

In the histological re-examination, I found a simple cyst in 20 cases (2 5 per cent) In large operative series of parotid tumours, simple cysts usually have an incidence of a few per cent, according to Kirklin *et al* (1951), Rauch (1959) and Beahrs *et al* (1960), from 1—4 6 per cent

The most common cyst is the retention cyst, it occurred in 15 of my cases A branchial cyst was found to be present in 5 cases This cyst formation is not so rare in the neck where it is generally located in front of the sternocleidomastoid muscle and is believed to arise from the second branchial cleft (Wilson 1955, Gore & Masson 1959) Branchial cysts of the parotid gland are, on the other hand, considered to arise from the first branchial cleft (Stark 1959, Hoffman 1960), and are regarded as extremely rare (Gore & Masson, Stark, Hoffman) Thus, Hoffman found only 12 cases of a branchial cyst of the parotid gland in his survey of the literature from 1908—1959 However, this anomaly is probably not as uncommon as was formerly believed since 5 cases (0 6 per cent) were found in the present material

Benign Lymphoepithelial Lesion

Benign lymphoepithelial lesion is the name proposed by Godwin for the lymph node lesion of the parotid gland whose histological features he defined in 1952 In his opinion the histogenesis is a combination of inflammatory and neoplastic factors According to Daly (1959) the most common view is that it is a reactive or inflammatory [illegible] Azzopardi & Smith (1959), among others have expressed the opinion that the benign lymphoepithelial lesion is a manifestation of Mikulicz's disease this [illegible] suggested by Kirklin *et al* (1951) Bauer & Bauer (1953) have



Fig 16 Benign lymphoepithelial lesion Photomicrograph × 130 Solid epithelial islands in lymphoid tissue

stated that this lesion is a histologically and clinically well defined neoplasm Lloyd (1946), Seifert & Geiler (1956) and Godwin regard the histogenesis to be the same as in papillary cystadenolymphoma, *i e*, a neoplastic proliferation of ectopic duct fragments in intraparenchymal lymph nodes

The histological picture is characterized by a dominant lymphoid component, containing solid epithelial islands (Fig 16) these consist of more or less sharply defined, relatively poorly differentiated epithelial cells

These features were identified at the histological re examination in 6 cases in my material (0 7 per cent) This incidence is in good agreement with the figure of 0 3 per cent given by Foote & Frazell (1954) and that of 0 4 per cent given by Beahrs *et al*

None of the 6 cases had been diagnosed primarily as benign lymphoepithelial lesion This can presumably be ascribed partly to the rarity of the tumour, and partly to the fact that it was defined as a separate entity as late as 1952 Before re-classification these tumours had been diagnosed as lymphadenitis (2 cases), chronic parotitis (1 case) and Mikulicz s disease (3 cases)

Because of the rarity of the tumour there is still great uncertainty about its clinical course It is however generally regarded as completely benign (Lloyd Godwin Foote & Frazell Grage *et al* 1961 b) and no case of metastases has been described Although recurrences have been reported they were probably — as in papillary cystadenolymphoma — not genuine recurrences, but new tumours originating in multiple anlagen

None of my 6 patients had a history of local pain or spontaneous paralysis of the facial nerve As far as the postoperative clinical course is concerned, no conclusions can be drawn from the present investigation This is because none of the 6 patients was followed up, since the primary diagnosis was a benign disease (lymphadenitis, chronic parotitis or Mikulicz's disease)

Lymph Node Hyperplasia

Lymph node hyperplasia with unspecific inflammation was found at histological re-examination of my material in 7 cases (0 9 per cent) This is in good conformity with the incidence of 1 1 per cent given by Beahrs *et al*

Thompson & Bryant (1950) and Seifert & Geiler (1956) have shown that lymph nodes are present intraparenchymally in the parotid gland In hyperplasia of lymph nodes lying deeply in the parenchyma, this is often interpreted as a neoplasm, and treated as such This applied to the 7 cases in my material

Lymphogranuloma

The name lymphogranuloma is used as a collective term for various kinds of pseudotumours, in which the lymph node involvement is a component of a disease complex If lymph nodes only at one site, e g in the parotid gland, are affected the condition may be interpreted as a neoplasm, and treated accordingly This applied in 5 cases in my material In four of them, the microscopical picture resembled that in tuberculosis or lymphogranulomatosis benigna (Schaumann's disease), and in one that in lymphogranulomatosis maligna (Hodgkin's disease)

Chronic Parotitis

In 15 patients in my material chronic parotitis was interpreted preoperatively as a neoplasm, and operated on for this reason Histological examination did not, however disclose any tumour tissue, but only an unspecific inflammatory reaction, with some destruction of the parenchyma and moderate to pronounced fibrosis

The differential diagnosis between a neoplasm and chronic parotitis is difficult in cases where no history of chronic, recurrent infections of the parotid gland is demonstrable and the inflammation is localized to a limited region of the gland Sialography is however an excellent differential diagnostic tool but it was not used in the 15 cases in question

CHAPTER VIII

Mucoepidermoid Carcinoma

Definition

Mucoepidermoid carcinoma did not become generally accepted as an independent type of tumour until the late nineteen-forties Although its recognition as a distinctive type was due largely to the work of Stewart *et al* (1945) and Linell (1948 its characteristic histological structures had been described much earlier *e g* by Schilling (1921) The name refers to the tumour's content of mucus-secreting and epidermoid cells

Histological Features

Description

The microscopical picture is characterized by clumps and strands of epidermoid cells, often fully squamous in character, as well as mucus-secreting, large, cylindrical epithelial cells The mucous cells are both diffusely scattered in the epidermoid cell regions, and collected in clumps, when they usually line mucus filled cystic spaces of varying size

The mucoepidermoid carcinoma also contains a third poorly differentiated type of cell These cells are known as intermediate since they are regarded as being an intermediate stage between the basal cells in interlobular salivary gland ducts and the epidermoid cells of the tumour (Stewart *et al*) The typical microscopical picture shows a mixture of these three cell types, *i e*, mucous epidermoid and intermediate

In the highly differentiated tumour, all three types of cell are present and there is, as a rule, pronounced squamous cell differentiation and numerous mucus-containing cystic spaces (Fig 17) In the poorly differentiated tumour, on the contrary, *squamous and mucous cells are less numerous and the intermediate cells* and poorly differentiated epidermoid cells predominate (Fig 18) Atypical cell forms are often present Consequently, the poorly differentiated mucoepidermoid carcinoma is apt to be confused with poorly differentiated adenocarcinoma and squamous cell carcinoma

Re-classification

My histological re-examination of the whole material disclosed the structures characteristic of mucoepidermoid carcinoma in tumours from 34 patients (4 2 per cent) The original diagnoses in these cases are listed in Table 16

It is evident from this table that 21 of the 34 tumours had been primarily diagnosed as mucoepidermoid carcinoma



Fig 17 Mucoepidermoid carcinoma Photomicrograph, × 130 Highly differentiated tumour with squamous cell differentiation and mucus producing cells, lining mucus filled cystic spaces

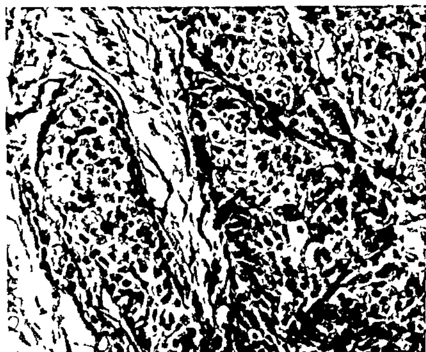


Fig 18 Mucoepidermoid carcinoma Photomicrograph, × 130 Poorly differentiated tumour with dominance of epidermoid polymorphous cells

Table 16 Mucoepidermoid carcinoma diagnoses before re-classification

Diagnosis		No of tumours
Mucoepidermoid carcinoma		21
Mixed tumour	semi malignant	4
	malignant	2
Papillary cystadenolymphoma	benign	5
	semi malignant	1
Benign cyst (unspecified)		1
	Total	34

In addition, mucoepidermoid carcinoma was originally classified in an equal number of cases as mixed tumour and papillary cystadenolymphoma respectively (6 tumours in each group) The often cystic structure of mucoepidermoid carcinoma is illustrated by the fact that 7 tumours were primarily diagnosed as some form of cyst, *i e*, papillary cystadenolymphoma (6 cases) and unspecified benign cyst (1 case)

Altogether 23 of the 34 tumours were primarily graded as malignant *i e* 21 as mucoepidermoid carcinoma and 2 as malignant mixed tumour Four originally classified as mixed tumours and one as papillary cystadenolymphoma were graded as semi malignant, whereas the remaining 6 were denoted as benign

Discussion

As early as 1921, the histological structures characteristic of mucoepidermoid carcinoma were described in detail together with illustrations by Schilling Tumours with similar histological features were subsequently described under various names, such as 'epithelioma a double metaplasie de la parotide (Masson & Berger 1924) "mixed epidermoid and mucus secreting carcinoma (De & Tribedi 1939) and 'schleimbildendes Epitheliom (Skorpil 1940 a) Although this type of tumour was differentiated histologically and clinically from other salivary gland tumours by Stewart *et al* in 1945 mucoepidermoid carcinoma is still designated in many classifications as a variant of other types (*e g* Edvall 1954 Mathis 1954, Redon 1960, Willis 1960) A number of these tumours in the present series were before re classification denoted as mixed tumour or papillary cystadenolymphoma (Table 16) According to Stewart *et al*, mucoepidermoid carcinoma is often found under other diagnoses as well, such as cylindroma', squamous cell carcinoma and unspecified adenocarcinoma The variation in the degree of differentiation (Figs 17 and 18) has led to confusion about the grade of malignancy of this type of tumour

In order to clarify the grade of malignancy of mucoepidermoid carcinoma several attempts have been made to divide this type of tumour into various subgroups, based on the degree of differentiation

Stewart *et al* divided mucoepidermoid carcinoma into two groups, one comprising highly differentiated benign tumours and the other poorly differentiated ma-

lignant tumours They did, however, point out that the borderline between the two groups is diffuse, and therefore difficult to draw Foote & Frazell and Sharp & Helsper (1960) introduced a third, intermediate group containing borderline cases between highly and poorly differentiated tumours Some authors, among them Marcial-Rojas & Sommers (1954), have expressed the view that only the relatively highly differentiated tumours should be denoted as mucoepidermoid tumours, whereas the poorly differentiated variants should be classified under the heading of undifferentiated or poorly differentiated carcinoma

Correlation Between Histological and Clinical Features

Results

The correlation between the histological features and clinical course of this type of tumour was studied in 23 patients, operated on in 1950—1957 The tumours were divided into two groups, according to the degree of differentiation Table 17 shows the results of a 5-year follow-up study of the correlation between the histological features (degree of differentiation) and the clinical course

It is seen in Table 17 that the material was divided into a group containing 20 highly differentiated tumours and a group containing 3 poorly differentiated tumours

Twenty one of the 23 patients were followed up for > 5 years The reason why the other 2 were not followed up is that the tumour was originally diagnosed as benign papillary cystadenolymphoma (Table 16)

One of the 18 patients with a highly differentiated mucoepidermoid carcinoma died of the tumour disease within 5 years, and one about 8 years after operation In Table 17 the latter patient is listed under the heading of 5 year survival She had a local recurrence, which showed infiltrative destructive growth towards the base of the skull, and proved to be inoperable One highly differentiated tumour was associated with metastasis within 5 years of operation The metastasis was to a cervical lymph node directly above the clavicle, and appeared about 2 years after primary operation (parotidectomy + neck dissection) After its removal, the patient survived and was asymptomatic for > 5 years

Table 17 Mucoepidermoid carcinoma correlation between histological and clinical features (5-year follow up period)

Degree of differentiation		No of patients		Died of	
		Total	Followed up	Intercurrent disease	Tumour disease
H		20	18	3	1
Po		3	3	0	2
	Total	23	21	3	3

Two of the 3 patients with a poorly differentiated mucoepidermoid carcinom died within 5 years of operation (after 1 and 2 years respectively) whereas th third survived and was asymptomatic after > 5 years All three patients hac metastases to regional cervical lymph nodes at primary operation In the two who died distant metastases as well developed about a year after operation in one case to the lungs and in the other to the pelvis

The calculated 5 year survival rate was 94 per cent in the highly differentiatec form of mucoepidermoid carcinoma, 33 per cent in the poorly differentiated form and 86 per cent in the whole group Totally 12 of the 18 followed up highly dif ferentiated tumours were primary Two of the 12 recurred Three patients with a highly differentiated tumour died of an intercurrent disease within 5 years of oper ation without demonstrable signs of the tumour disease one of them 3 years after operation and two 4 years after

In the material followed up for > 5 years there was a history of preoperative pain in 2 of 18 patients with a highly differentiated tumour and in 1 of 3 with a poorly differentiated tumour All three patients were alive and without symptoms > 5 years after operation

None of the tumours in the highly differentiated group gave rise to spontaneous paralysis of the facial nerve whereas this applied in 1 of the 3 patients with a poorly differentiated tumour He died of the tumour disease 1 year after the onset of paralysis

Discussion

Controversy about the grade of malignancy of mucoepidermoid carcinoma is to be ascribed mainly to the fact that this type of tumour is comparatively rare (an in cidence of 4 2 per cent in my material and of 5—12 per cent according to *e g* Stewart *et al* Rawson *et al* 1950 Foote & Frazell Bruzelius *et al* and Beahrs *et al*) It is therefore difficult to correlate the histological features of tumours in different stages of differentiation to their clinical course The present material was divided into two groups *i e* highly differentiated and poorly differentiated tu mours The incidence of recurrence of highly differentiated tumours after primary operation was found to be 16 6 per cent (2 of 12) As a comparison it can be

Metastases	Local recurrence total	5 year survival: Local recurrence	Asympto-matic	Total	Observed %	Calculated %
1	4	4	10	14	77 7	94 4
3	1	0	1	1	33 3	33 3
4	5	4	11	15	71 4	85 7

mentioned that the corresponding incidence in primarily operated benign mix tumours of the parotid was 0.3 per cent (1 of 312). Moreover, in contrast Stewart *et al.*, I found that the highly differentiated form was associated with bot metastases and death in the tumour disease.

This implies that the highly differentiated form of mucoepidermoid carcinom is definitely malignant. Consequently, it should not be denoted as benign — done by *e.g.* Stewart *et al.* and Marcial-Rojas & Sommers — nor as semi-malignt (Rauch 1959, Glaser 1962, Hellner 1962, Morehead 1962, among others).

A comparison between the highly differentiated and poorly differentiated grou discloses a marked difference with respect to the incidence of metastases and 5-ye survival rate. Thus, the latter group shows a considerably higher grade of ma lignancy than the former one. This does, to some extent, motivate dividing th type of tumour into two groups of malignancy, *i.e.*, low grade and high grade, suggested by Bruzelius *et al.* and Beahrs *et al.*, among others.

Although separation of mucoepidermoid carcinomas into two groups on the bas of the degree of differentiation is of certain clinical importance, no definite prog nostic conclusions can be drawn from their assignation to one or the other grou Stewart *et al.* stated that the poorly differentiated tumours are recurrences of th highly differentiated ones. This is not in agreement with the observations in th present series, in which all 3 poorly differentiated tumours were primary, and a 8 secondary tumours were highly differentiated.

The difficulty of defining the two groups histologically in any uniform way evident from their greatly varying distribution in different series. Thus, the highl differentiated group has been stated to comprise 92 per cent of the mucoepidermo carcinomas (Beahrs *et al.*), 50 per cent (Foote & Frazell) and 21 per cent (Bruze lius *et al.*). In my material, the incidence is 91 per cent.

According to Stewart *et al.* and Foote & Frazell, as well as Rauch and Glaser among others, there is also a distinct difference between the two categories wit respect to the symptomatology. This is apparent from the incidence figures fo preoperative pain and paralysis of the facial nerve. The latter has not been dem onstrated earlier in association with a highly differentiated tumour. This als applied in my series, in which only one poorly differentiated tumour was responsibl for spontaneous facial nerve paralysis. In mucoepidermoid carcinoma, this prove to be as severe a prognostic sign as in other malignant parotid tumours in the ma terial, *i.e.*, the patient died of the tumour disease within 5 years.

Despite the difficulty of making a uniform, histological distinction between th high-grade and low-grade malignant tumours, most authors use this grading in ar account of their therapeutical results (*e.g.* Stewart *et al.*, Foote & Frazell, Rauch Glaser). No comparison can be made between different series with respect to th results in the two groups, in view of the lack of uniformity in their histologica definition. Consequently, if any comparison is to be made, the mucoepidermoi carcinomas must be assembled in a single group.

Summary

Mucoepidermoid carcinoma — the type of tumour defined by Stewart *et al* is found to exhibit a marked variation with respect to the degree of differentiation The highly differentiated tumours have a characteristic histological structure and are easily diagnosed The poorly differentiated ones on the contrary are apt to be confused with poorly differentiated adenocarcinoma and squamous cell carcinoma In the present investigation, even the highly differentiated form of this tumour type is found to be malignant

CHAPTER IX

Adenoid Cystic Carcinoma

Definition

Adenoid cystic carcinoma was defined as an independent type of tumour by Quattlebaum *et al* in 1946, under the name of "adenocarcinoma of cylindroma type" The authors proposed this name both to stress the malignancy of the tumour and to distinguish it from the diffuse cylindroma concept, without abandoning the histologically descriptive term cylindroma However, during the past decade, the term *adenoid cystic carcinoma — suggested by Spies as early as 1930, and adopted by* Foote & Frazell in 1954 — has won increasing acceptance

Histological Features

Description

Adenoid cystic carcinoma has a characteristic histological picture, in the form of *epithelial islands of varying size, composed of small uniform cells with dark nuclei* and little cytoplasm These epithelial islands contain myxoid usually hyalinized areas (cylinders), giving rise to the typical cribriform structures (Fig 19 A) The myxoid areas of the adenoid cystic carcinoma can be easily distinguished from the myxoid components of a mixed tumour by the clear demarcation between the epithelial and the myxoid intercellular areas In a mixed tumour, on the contrary, the epithelial cells are scattered in the myxoid substance

Alternating with the cribriform structures are purely cystic areas, as well as solid fields Another typical feature is infiltrative growth into surrounding tissues, particularly into perineural lymph spaces (Fig 19 B)

Re-classification

At my histological re-examination of the whole operative material, I found the structures characteristic of adenoid cystic carcinoma in 19 of 802 patients (2 3 per cent) The majority of these tumours had, however, originally been classified under *completely different diagnoses, as can be inferred from Table 18*

It is evident from Table 18 that, before the histological re-examination and re-classification most of the adenoid cystic carcinomas (14 of 19) had been diagnosed *as mixed tumours One of the 14 had been denoted as benign 6 as semi malignant* and [illegible] nant Three of the 4 tumours operated on in 1958—1962 were primarily [illegible] d as adenoid cystic carcinoma and the fourth as poorly differentiat[illegible] carcinoma



Fig 19 Adenoid cystic carcinoma

A Photomicrograph × 50 Typical cribriform structures



B Photomicrograph × 130 Invasive perineural growth

Table 18 Adenoid cystic carcinoma diagnosis before re-classification

Diagnosis		No of tumours
Adenoid cystic carcinoma		3
Poorly differentiated anaplastic carcinoma		1
Papillary cystadenolymphoma		1
Mixed tumour	benign	1
	semi malignant	6
	malignant	7
	Total	19

Discussion

Cylindromatous structures have been demonstrated in a number of tumour types clearly distinguished from each other, and of a varying grade of malignancy, such as adenoid cystic carcinoma (Quattlebaum *et al*), adamantinoma (Naumann 1958), basal-cell carcinoma (Krompecher 1918), mixed tumour (Ahlbom 1935, Dockerty & Mayo 1942, Gunnel 1956) and hydradenoma or "turban tumour" (Boyd 1953) These types of tumour were earlier denoted — and are still denoted in many classifications — as cylindroma This diffuse collective term was introduced by Billroth as early as 1859, and is used nowadays to a great extent to denote adenoid cystic carcinoma only (*e g* Rawson *et al* 1950, Kirklin *et al* 1951, Rauch 1959, Glaser 1962) However, according to Soboroff (1959), cylindroma is a term which gives no information about the malignancy of this type of tumour

To stress the difference from the diffuse cylindroma concept, von Albertini (1955) denoted adenoid cystic carcinoma as "reine Cylindrome", and Redon (1960) as "cylindrome pur"

It is thus evident that the nomenclature varies greatly, which gives rise to some confusion This could be avoided if the cylindroma concept were to be discarded

Microscopically, adenoid cystic carcinoma has proved to be clearly distinguished from other tumours with cylindromatous structures, *e g* by the absence of structures typical of other types, and by its infiltrative growth into surrounding tissues, particularly perineurally The presence of myxoid, chondroid or fibroid components concurrently with cylindromatous structures implies that the tumour should not be denoted as an adenoid cystic carcinoma, but as a true mixed tumour instead Moreover, as already pointed out, the myxoid areas in an adenoid cystic carcinoma can be distinguished from the myxoid components of a mixed tumour (*e g* Thackray & Lucas 1960) Totally 103 of the 360 true mixed tumours without infiltrative destructive growth in my operative series from 1950—1957 exhibited cylindromatous structures This explains why so many of the adenoid cystic carcinomas in the series (14 of 19) were primarily diagnosed as mixed tumours Many authors are in fact still of the opinion that adenoid cystic carcinoma does not warrant separation from the mixed tumours (*e g* Willis 1950, 1960)

The [illegible] component of adenoid cystic carcinoma sometimes forms cystic

structures, and sometimes solid areas For this reason Ringertz (1938) divided cylindromas into two subgroups, namely, solid basalioma and adenoid cystic epithelioma The presence of solid areas explains why one of the tumours in my material was originally diagnosed as poorly differentiated anaplastic carcinoma With better knowledge of the histological features of adenoid cystic carcinoma it is relatively easy to diagnose, in view of the characteristic picture This is borne out by the fact that the 15 cases operated on in 1950—1957 had been primarily classified as other types of tumour, whereas 3 of the 4 operated on in 1958—1962 were primarily diagnosed as adenoid cystic carcinoma

Correlation Between Histological and Clinical Features

Results

My histological re examination of the material disclosed the microscopical features characteristic of adenoid cystic carcinoma in tumours from 15 patients operated on in 1950—1957

All 15 patients were followed up for > 5 years, the results are listed in Table 19 During this period, none of them died of an intercurrent disease, whereas 2 died of the tumour disease A local recurrence occurred in one of these two cases The other local recurrence noted in the table took place in a patient who did not die of the tumour disease until 7 years after operation, she is therefore listed under 5 year survival

Metastases appeared within 5 years in 3 patients, 2 of whom died during the observation period The third survived > 6 years after operation (last follow up examination in January 1964), with histologically verified skeletal metastasis to the cranium Distant metastases were present in all 3 cases in the first two to the lungs and in the third to the skeleton

Eleven of the 15 patients survived and were asymptomatic during the observation period The observed and the calculated 5 year survival rate are the same (87 per cent), since no patient died of an intercurrent disease during this time In addition to the patients who died during the 5 year observation period, one died of the tumour disease about 7 years after operation In this case metastases to the lungs were present, but they were not detected until a few months before death

None of the 15 patients listed in Table 19 had a history of local preoperative pain Spontaneous paralysis of the facial nerve appeared in two of these patients one died 2 years after its onset and the other 3 years after it An additional 4 patients with adenoid cystic carcinoma were operated on in 1958—1962 so that the total material comprises 19 patients There was a history of local pain preoperatively in 1 of the 19, and of spontaneous paralysis of the facial nerve in 3 of the 19

Discussion

The results of the present investigation show that tumours with the histological structures typical of adenoid cystic carcinoma are malignant The incidence of recurrence metastasis and survival reported in the literature varies greatly with the

Table 19 Adenoid cystic carcinoma correlation between histological and clinical features (5-year follow up period)

No of patients		Died of			
Total	Followed up	Intercurrent disease	Tumour disease	Metastases (total)	Local recurrence (total)
15	15	0	2	3	2

definition of this type of tumour Consequently, my incidence figures can be compared only with those in series where adenoid cystic carcinoma was also defined according to the strict criteria of Quattlebaum *et al*

This type of tumour is comparatively rare Thus, in the present material it comprised 2 3 per cent of all parotid tumours, and ranged from 1—5 per cent in the series reported by Rawson *et al* (1950), Kirklin *et al* (1951), Frazell (1954), Bruzelius *et al* (1957), Beahrs *et al* (1960), Nanson (1960), Sharp & Helsper (1960) and Shindel & Markowicz (1961), among others

In view of the relatively uncommon location of this type of tumour to the parotid gland, there have been difficulties in obtaining a clear picture of its clinical course However, the present correlation study showed that adenoid cystic carcinoma — in contrast to mixed tumours with cylindromatous structures — is a malignant type of tumour, associated with metastasis and death During a 5-year follow up period, the calculated survival rate was 87 per cent, and the incidence of metastases 20 per cent All metastases were distant metastases, and no case of metastases to regional lymph nodes in the neck was detected As a comparison, it can be mentioned that Quattlebaum *et al*, Kirklin *et al* and Frazell found this type of tumour to metastasize in 25—50 per cent of cases, and that Quattlebaum *et al* and Beahrs *et al* reported a 5 year observed survival rate of 60 and 76 per cent, respectively The incidence of local recurrence was 13 per cent in my material, whereas Quattlebaum *et al* and Frazell stated the corresponding incidence to be 75 and 50 per cent, respectively

Many authors have stated that this type of tumour has a special tendency to perineural invasion (*e g* Dockerty & Mayo 1942, Quattlebaum *et al*, Bauer & Bauer 1953, Ross 1955, Thackray & Lucas 1960, Stewart 1961) This would explain the high incidence of local pain and of spontaneous paralysis of the facial nerve According to Quattlebaum *et al*, Kirklin *et al* and Rauch, as well as Beahrs *et al* and Glaser among others, 25—50 per cent of all adenoid cystic carcinomas give rise to local pain, whereas — according to Kirklin *et al* — spontaneous facial nerve paralysis appears in about 25 per cent of the cases These incidence figures are much higher than those in my series, in which there was no history of pain in any of the cases followed up for >5 years (but in 1 of the total 19 cases) Spontaneous paralysis of the facial nerve occurred in 13 per cent (2 of 15) and proved to imply a hopeless prognosis

5 year survival					
Metastases	Local recurrence	Asympto-matic	Total	Observed %	Calculated
1	1	11	13	80	

Summary

The present investigation has shown that adenoid cystic carcin[illegible] type of tumour described by Quattlebaum *et al* — is a definite entity both histologically and clinically, and that it is malignant It is emphasized that a specially important point is its distinction from the diffuse cylindroma concept which includes mixed tumours with cylindromatous structures

CHAPTER X

Acinic-Cell Carcinoma

Definition

Acinic-cell adenocarcinoma was the name given by Godwin *et al* to the tumour which they distinguished from other types of parotid tumour in 1954 "Acinic cell" referred to the great resemblance of the tumour cells, both microscopically and histochemically, to normal acinar cells "Adenocarcinoma" was used because the apparently benign histological structures are not infrequently associated with clinically malignant behaviour Nowadays, the most usual term is, however, acinic-cell carcinoma (Beahrs *et al* 1960, Grage *et al* 1961 a, Glaser 1962, among others)

Histological Features

Description

Acinic-cell carcinoma is composed of acinar-like cells, which may be closely packed in solid fields, or form glandular structures Stroma and blood vessels are scanty, whereas numerous intercellular vacuoles, containing plentiful secretion, are present The individual tumour cell is as large as the normal acinar cell, or usually larger than it, and has a distinct cell membrane and small, dark nucleus No other components found in other types of tumour, such as mixed tumours, occur Nor are there, as a rule, any ductal structures The histological structures typical of an acinic cell carcinoma are shown in Figure 20.

Re-classification

In my histological re-examination of the present material, I found tumours exhibiting the characteristic features of acinic-cell carcinoma in 36 of 802 patients (4 5 per cent) In 2 of the 36 cases, both the right and the left parotid gland were involved

It can be inferred from Table 20 that, before re-classification, the great majority of these tumours had been classified under a variety of other diagnoses The 13 acinic-cell carcinomas treated from 1960 onwards were, however, primarily diagnosed as such In 1950—1959, 23 acinic-cell carcinomas were operated on, only one of them (operation in 1959) was originally classified as this type of tumour Totally 18 of the remaining 22 cases were classified as a mixed tumour or as an adenoma of a varying grade of malignancy Thus, only one of these 18 tumours was denoted as

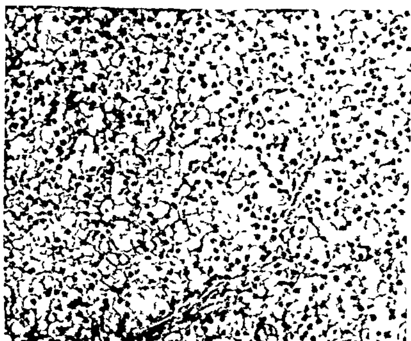


Fig. 20. Acinic-cell carcinoma. Photomicrograph × 130. Homogeneous tumour structure with acinar like cells containing small dark nuclei.

benign, whereas 12 were denoted as semi malignant and 5 as malignant. Two of the remaining acinic cell carcinomas operated on in 1950—1959 were originally classified as semi malignant papillary cystadenomas and 2 as unspecified adenocarcinomas.

Table 20. Acinic-cell carcinoma: diagnoses before re-classification.

Diagnosis		No. of tumours
Mixed tumour	benign	1
	semi malignant	6
	malignant	4
Papillary cystadenoma	benign	0
	semi malignant	2
	malignant	0
Adenoma	benign	0
	semi malignant	6
	malignant	1
Adenocarcinoma (unspecified)		2
Acinic-cell carcinoma		14[1]
	Total	36

[1] 13 of these 14 cases were operated on in 1960—1962.

Discussion

Acinic cell carcinoma exhibits a highly characteristic microscopical appearance which easily separates this type of tumour from other tumours of the parotid gland These characteristic features were actually described long before Godwin *et al* in 1954 defined acinic cell carcinoma as an independent type of tumour However these earlier histological descriptions were based only on isolated cases No clinical conclusions could therefore, be drawn from the histological picture This implied that the tumour was not regarded as a distinct type, but was denoted as a variant of other types such as mixed tumour and papillary cystadenolymphoma

It is evident from Table 20 that most of the acinic cell carcinomas in the present series were originally classified as a mixed tumour adenoma or papillary cystadenolymphoma of varying malignancy However, from 1960 onwards every such tumour was primarily diagnosed as an acinic cell carcinoma This indicates that once this tumour had been recognized as a separate type no difficulty was encountered in identifying it in view of the characteristic histological structures Nevertheless, acinic cell carcinoma is still often regarded as a variant of other types *e g* mixed tumour (Corridan 1956 Willis 1960 among others), or papillary cystadenolymphoma (Bauer & Bauer 1953)

In 2 of my 36 patients the acinic-cell carcinoma was bilateral This is remarkable since — with the exception of papillary cystadenolymphoma — bilateral parotid tumours have exceedingly seldom been demonstrated (*e g* Kaliampetsos & Bonmann 1959) As an example it can be mentioned that there was not a single case of bilateral occurrence in Foote & Frazell s series of 493 mixed tumours and only one in the present series of 569 such tumours I have been unable to trace any case of bilateral acinic cell carcinoma in the literature in addition to that reported by Bauer & Bauer in 1953 — I have previously given an account of the two bilateral tumours of this type in the present material (Diamant *et al* 1961)

Correlation Between Histological and Clinical Features

Results

My histological re examination of the material revealed the structures characteristic of acinic cell carcinoma in 36 patients 21 of whom were operated on in 1950—1957 The 5 year results of surgical treatment were studied in these 21 cases (Table 21)

It can be inferred from Table 21 that the apparently innocent structures in an acinic cell carcinoma are associated with clinical signs of malignancy Thus 2 of 21 patient died of the tumour disease within 5 years and in both cases metastases were demonstrable In one of these cases there were both metastases to regional cervical lymph nodes and distant metastases (to the lungs and skeleton) In the other ca[illegible]e [illegible] distant metastases (to the liver) were recorded Metastases were found o[illegible] the [illegible] ase

In add[illegible] the t[illegible]o patients who died of the tumour disease two died of an

Table 21 Acinic cell carcinoma correlation between histological and clinical features (5-year follow up period)

No of patients		Died of			Local recurrence (total)	5 year survival				
Total	Followed up	Intercurrent disease	Tumour disease	Metastases		Local recurrence	Asymptomatic	Total	Observed %	Calculated %
21	21	2	2	2	4	2	15	17	80 9	89 5

intercurrent disease during the observation period 2 and 3 years respectively, after operation Thus, 17 of the 21 patients lived for > 5 years following initial treatment after admission This gives an observed 5 year survival rate of 81 per cent whereas the calculated 5 year survival rate is higher (90 per cent), owing to the deaths in intercurrent diseases

Altogether 18 of the 21 followed up cases were primary, and 3 were secondary Local recurrences took place in 3 patients in the former group, and in one in the latter This implies that totally 4 of the 21 tumours were associated with local recurrences Two of the patients with recurrences died within 5 years, whereas the other two lived for > 5 years after operation and are therefore listed under 5 year survival

There was a history of preoperative pain in the tumour region in 3 of the 21 patients accounted for in Table 21 Paralysis of the facial nerve unconnected with any surgical intervention appeared in 2 patients both of them died (1 and 2 years respectively after the onset of paralysis)

Discussion

Histologically acinic cell carcinoma is a highly characteristic type of tumour Despite this great uncertainty exists regarding its clinical behaviour This uncertainty can be ascribed partly to the fact that the tumour has been recognized as an entity only in recent years and partly to its rarity Thus Foote & Frazell as well as Rauch and Beahrs *et al* stated that it comprises about 3 per cent of all tumours of the parotid gland The largest series of acinic cell carcinomas with an observation period of > 5 years that I have been able to find in the literature consists of 19 cases (Beahrs *et al*) The present material comprises 36 cases of which 21 were followed up for > 5 years

In view of its microscopical features this type of tumour has generally been considered earlier as benign which is apparent from the nomenclature Examples are epithelioma glandulaire (Masson 1924) parathyreoideaähnliche Geschwulst (Franssen 1932 Huckel 1933) and glycogen rich clear cell adenoma (Corridan 1956 It is evident from the present correlation study that acinic cell carcinoma is in fact a malignant type of tumour which is responsible for metastases and death According to Rauch metastases are extremely uncommon but have nevertheless been described by Godwin *et al* and Grage *et al* (1961 a among others

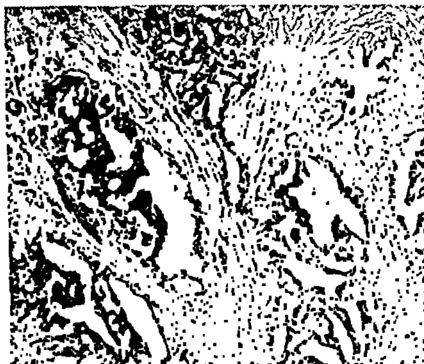


Fig. 21. Mucus-producing adenopapillary carcinoma. Photomicrograph, × 50. Cystic and adenopapillary structures.

Re-classification

In the histological re-examination of the whole material, I found tumours with the structures typical of mucus-producing adenopapillary carcinoma in 12 patients.

It can be inferred from Table 22 that 6 of the 12 tumours hade been primarily diagnosed as adenocarcinoma of some kind, i.e., 2 as adenoid cystic carcinoma, 1 as unspecified adenocarcinoma, and 3 as mucus-producing adenopapillary carcinoma. The remaining 6 tumours had been classified as mixed tumours or adenoma.

Since 2 of the mixed tumours and one of the "salivary-gland adenomas" had been primarily classified as malignant, totally 9 of the 12 tumours had been denoted as malignant. The 3 remaining tumours had been denoted as semi-malignant.

Correlation Between Histological and Clinical Features

Results

Seven of the 12 patients with a mucus-producing adenopapillary carcinoma were operated on in 1950–1958 and could therefore be followed up for > 5 years. The results are shown in Table 23.

The correlation study showed that this type of tumour is malignant. Thus, 2 of 7 patients with a mucus-producing adenopapillary carcinoma died of the tumour disease within 5 years. Metastases were demonstrable only in these two patients, in the form of both metastasis to regional cervical lymph nodes and distant metastases.

Table 23 Mucus producing adenopapillary carcinoma correlation between histological and clinical features (5-year follow up period)

No of patients		Died of			Local recurrence (total)	5 year survival				
Total	Followed up	Intercurrent disease	Tumour disease	Metastases		Local recurrence	Asymptomatic	Total	Observed %	Calculated %
7	7	0	2	2	3	1	4	5	71 4	71 4

The observed and the calculated 5 year survival rate are the same (71 per cent) since no patient died of an intercurrent disease Local recurrences appeared in 3 cases *i e*, in the two patients who died of the tumour disease and in one patient who, after operation of the recurrence, survived and was asymptomatic for > 5 years This case is therefore listed under 5 year survival

Five of the 7 patients had a primary tumour, 4 of them were alive and without symptoms > 5 years after operation The remaining patient died of the tumour disease within one year of operation

No patient complained of local pain preoperatively Spontaneous paralysis of the facial nerve appeared in 2 of the 7 patients Both of them died of the tumour disease (1 and 3 years, respectively, after the onset of paralysis)

Discussion

In the present investigation, mucus producing adenopapillary carcinoma was found to have characteristic microscopical features Although this type of tumour was distinguished from other types of parotid tumour by Kirklin *et al* (1951), among others, in most classifications it is still listed under the diffuse collective term adenocarcinoma This perhaps explains why, in my material the tumour was so often denoted as a variant of some other type such as mixed tumour, adenoma or adenoid cystic carcinoma (Table 22)

The incidence of recurrence metastasis and mortality in the present material shows that mucus producing adenopapillary carcinoma is a type of parotid tumour of relatively high grade malignancy

The incidence of spontaneous paralysis of the facial nerve was high (about 29 per cent) As in the other types of malignant parotid tumour I have described this proved to be associated with a hopeless prognosis

Summary

Mucus producing adenopapillary carcinoma is found to be a type of tumour with histologically characteristic features In this material it has proved to be malignant and the grade of malignancy seems to be higher than that of the highly differentiated form of mucoepidermoid carcinoma acinic-cell carcinoma and adenoid cystic carcinoma

lae The cell picture and infiltrative growth give an impression of malignancy, and 4 of these 5 tumours had, in fact, been primarily diagnosed as malignant

In view of the extremely limited material, no definite conclusions can be drawn from the results of the present correlation study However, because of the incidence of recurrence and metastasis, as well as of the mortality rate, trabecular adenocarcinoma appears to be a highly malignant type of tumour As in other malignant tumours of the parotid gland spontaneous paralysis of the facial nerve was found to imply a hopeless prognosis

Summary

Trabecular adenocarcinoma is found to be an exceedingly rare, poorly differentiated and highly malignant tumour of the parotid gland

CHAPTER XIII

Solid Anaplastic Adenocarcinoma

Definition

Solid anaplastic adenocarcinoma is a rare form of adenocarcinoma (in the present material 1 1 per cent of the total tumours), with a name drawing attention to its histological characteristics In most classifications it is not denoted as an independent type of tumour, but is found as a subgroup of a larger collective group, such as 'miscellaneous forms of adenocarcinoma' (*e g* Foote & Frazell 1954 Bruzelius *et al* 1957) I have, however, chosen to differentiate this type of tumour from other forms of adenocarcinoma, and to make a separate study of its histological and clinical features

Histological Features

Description

Solid anaplastic adenocarcinoma is composed of small polymorphous undifferentiated epithelial cells, compactly put together They lie closely in bands or clumps without any characteristic pattern (Fig 23) The cell masses are separated by streaks of connective-tissue stroma, hyalinized in places As a rule the tumour shows diffuse infiltrative destructive growth into surrounding tissues

Re-classification

In my histological re examination of the whole material I found tumours with the structures characteristic of solid anaplastic adenocarcinoma in 9 patients As shown in Table 25 most of these tumours had previously been given completely different diagnoses

This type of tumour exhibits a clearly malignant histological picture as can be inferred from the fact that all 9 tumours were primarily diagnosed as malignant

Table 25 Solid anaplastic adenocarcinoma diagnoses before re classification

Diagnosis		No of tumours
Mixed tumour malignant		6
Adenoid cystic carcinoma		1
Poorly differentiated carcinoma		1
Solid carcinoma		1
	Total	9



Fig 23 S ... micrograph, × 50 Cords and clumps of closely pac ...

Six of the 9 cases had been originally denoted as mixed tumours, despite the absence of structures characteristic of this tumour type The other 3 had, however, been diagnosed as some form of carcinoma The primary diagnosis of adenoid cystic carcinoma in one case is easily understandable, in view of the microscopical features of the solid areas in this type of tumour However in adenoid cystic carcinoma, the typical cribriform pattern is generally seen in some part of the tumour Moreover, its cells are less polymorphous than those in solid anaplastic adenocarcinoma

Correlation Between Histological and Clinical Features

Results

Altogether 7 of the 9 patients with solid anaplastic adenocarcinoma were operated on in 1950—1957 and could therefore be followed up for > 5 years The results are seen in Table 26

Three of the 7 patients died of the tumour disease within 5 years of operation, and one not until 9 years after operation Local recurrences took place in all 4 patients within 5 years of operation the remaining 3 survived without symptoms for > 5 years Since there was no death from an intercurrent disease during the observation period the observed and the calculated 5-year survival rate are the same (57 per cent

Metastases were demonstrable within 5 years in 3 of 7 cases In all 3, the metasta-

Table 26 Solid anaplastic adenocarcinoma correlation between histological and clinical features (5-year follow-up period)

No of patients		Died of			Local recurrence (total)	5-year survival				
Total	Followed up	Intercurrent disease	Tumour disease	Metastases		Local recurrence	Asymptomatic	Total	Observed %	Calculated %
7	7	0	3	3	4	1	3	4	57.1	57.1

ses were to regional cervical lymph nodes, in 2 of these patients there were in addition, metastases to the lungs Metastases to the lungs developed in an additional patient, but not until 7 years after operation

One of the 7 patients had a history of pain in the tumour region, and spontaneous paralysis of the facial nerve occurred in 2 cases Both these patients died of the tumour disease (barely 1 year and just over 2 years respectively after the onset of paralysis)

Discussion

Solid anaplastic adenocarcinoma shows a characteristic histological picture There may however, be difficulty in making a differential diagnosis from trabecular adenocarcinoma Both types of tumour are poorly differentiated, but the former lacks the trabecular pattern, and the tumour cells are small and not as polygonal as in the latter type

Microscopically, solid anaplastic adenocarcinoma gives a definitely malignant impression This is evident from the fact that all the present 9 cases were primarily denoted as malignant tumours — although under various diagnoses (Table 25) The correlation study showed that this type of tumour — in view of its high incidence of local recurrence, metastasis and mortality — is highly malignant in comparison to the highly differentiated form of mucoepidermoid carcinoma, acinic-cell carcinoma and adenoid cystic carcinoma Spontaneous paralysis of the facial nerve appeared in 2 of 7 cases and proved, as in other malignant parotid tumours, to be accompanied by a hopeless prognosis

Summary

Solid anaplastic adenocarcinoma is found to be a rare poorly differentiated and highly malignant type of parotid tumour

CHAPTER XIV

Miscellaneous Types of Malignant Tumours

In my histological re-examination of the whole material, I found in 6 patients an additional three types of malignant tumour, i.e., squamous-cell carcinoma, melanoma malignum and fibrosarcoma. Since the histological and clinical features of these tumours are well known from other localizations, only a brief account of them will be given here.

Squamous-Cell Carcinoma

In the whole material comprising 802 patients, a tumour with the histological structures characteristic of squamous-cell carcinoma was found in only one patient (0.1 per cent). The incidence of this type of tumour ranges in different series of parotid tumours from 1.4 per cent (Beahrs *et al.* 1960) to 3.4 per cent (Frazell 1954). Bruzelius *et al.* (1957) did not have a single case of squamous-cell carcinoma in their series of 180 parotid tumours.

The only patient with squamous-cell carcinoma in my material was alive and asymptomatic > 5 years after operation (total radical parotidectomy).

Melanoma Malignum

The histological features typical of melanoma malignum were found in 2 cases (0.2 per cent), an incidence in good agreement with the figures of 0.3—0.4 per cent given by various authors (e.g. Kirklin *et al.* 1951, Edvall 1954, Beahrs *et al.* 1960). According to Rauch (1959), this type of tumour does not occur in any other salivary gland than the parotid. This may be due to the parotid being the only salivary gland to contain intraparenchymal lymph nodes, and to the melanoma malignum probably not being primary in the parotid gland but a metastasis to its lymph nodes.

Both these tumours in my material were, in fact, regarded by the pathologist to be metastases [illegible] parotid lymph nodes. In one case no primary focus could be traced. The other [illegible] had, a year before removal of the parotid tumour, been operated on for a [illegible] of the cheek on the same side (the tumour was not, however, sent for micr[illegible] examination). *The former patient survived for > 5 years after* operation [illegible] whereas metastases appeared in the latter, and he died of the [illegible] year of operation.

Fibrosarcoma

Three patients (0.4 per cent) were operated on for a tumour which, at the histological re-examination, proved to be a fibrosarcoma. This incidence is in good conformity with that of 0.3—0.6 per cent reported by Rawson *et al.* (1950) and Edvall, among others. One of these patients died of the tumour disease with metastases within one year of operation, whereas the other two survived without a recurrence for > 5 years.

Summary

Miscellaneous types of malignant tumour comprise some rare forms of parotid tumour (squamous-cell carcinoma, melanoma malignum and fibrosarcoma), whose histological features are well known from other localizations. No definite conclusions can be drawn regarding their clinical course when they involve the parotid gland, since the number of tumours in each group is too small.

General Discussion

If a classification of tumours is to be of practical value, it should allow clinical conclusions to be drawn from the histological features of the various types of tumour The types described in Chapters IV—XIV are well-defined histologically A study of the correlation between histological features and clinical course permitted a division into benign and malignant tumours Such a classification of parotid tumours — based on histologically distinct types, that could be denoted as either benign or malignant — should be useful from the therapeutical point of view The present classification is based on that proposed by Foote & Frazell (1954), and adopted by *e g* Bruzelius *et al* (1957), but which has not won any widespread acceptance outside the U S A This is probably due to the fact that it has not yet been possible to verify the clinical value of this classification, mainly because earlier investigations have been founded on too small or incompletely analyzed series

By means of a follow up study of a series from 1950—1957, the clinical course of the various tumour types could be analyzed, after histological re-classification of the material The results showed that the types of tumour that are well defined histologically are also well defined clinically

In 1950—1957, the great majority of the parotid tumours were treated radiosurgically, *i e*, by a combination of irradiation and surgical therapy The extent of the surgical procedure varied Parotidectomy (total or partial) was undertaken only in the presence of suspected or established malignancy Thus, the treatment was not uniform In view of this factor, as well as of the greatly varying preoperative duration of the tumour and possible earlier operations before the first operation at the Department of Otolaryngology, Karolinska Sjukhuset, no definite conclusions about the malignancy of the various tumours can be drawn from the incidence of local recurrence

Metastasis and mortality in the tumour disease are generally used as criteria in grading the malignancy These criteria may, however, also imply some uncertainty, because of the aforementioned factors The calculated 5 year survival rate is based on the annual mortality in the tumour disease, and is perhaps the best criterion of the malignancy of a type of tumour It was therefore used for evaluation of the malignancy in the present material Even if certain of the groups of malignant tumours are relatively small, a study of the calculated 5-year survival rate gives some idea of the malignancy of the various types of tumour

My study of the correlation between histological and clinical features allowed the group of mixed tumours to be divided into two subgroups, namely, benign and malignant In addition the other types of tumour in the material could be specified as benign and malignant respectively Owing to the earlier diffuse definition of parotid tumours, great uncertainty existed regarding the malignancy of the various

types This was reflected in the large number denoted as semi malignant After re classification most of these proved to be mixed tumours

Although the mixed tumour group has become increasingly distinctly defined from the histological aspect in recent years the concept of semi malignancy is still used precisely in connexion with this type of tumour This indicates that these tumours are particularly difficult to evaluate as far as malignancy is concerned As a rule, the whole mixed tumour group continues to be denoted as semi malignant (e g Agner & Nielsen 1956, Rauch 1959, Glaser 1962 Hellner 1962) or is only partly semi malignant (e g Edvall 1954, Mylius 1960 Morehead 1962)

High cellularity, predominance of the epithelial component cylindromatous structures, multiple foci and incomplete encapsulation have successively become more widely accepted as signs of malignancy in mixed tumours For example before re classification of the present material, > 50 per cent of the mixed tumours were denoted as semi malignant because of the presence of one or more of these criteria

It could be demonstrated in my study of the correlation between the histological features of the mixed tumours and their clinical course that the aforementioned criteria of semi malignancy were not, in fact associated with a higher incidence of local recurrence than were the clearly benign structures Nor were metastases and death in the tumour disease noted when these criteria were fulfilled This implies that the concept of semi malignancy in mixed tumours lacks justification Considerable practical consequences are involved since the earlier routine life long follow up examinations of all patients with semi malignant mixed tumours will no longer be required The investigation showed that a mixed tumour is malignant only when there is infiltrative destructive growth into surrounding tissues Consequently, the aforementioned frequent re-examinations can be confined to these rare cases

In the present material the mixed tumour group comprised about 70 per cent of all tumours of the parotid gland In view of the lack of justification of the term semi malignancy it could be divided into two distinctly separated groups *i e* a group of benign tumours containing about 98 per cent and a group of malignant tumours containing about 2 per cent

After re classification and apart from the mixed tumour group (70 9 per cent the benign tumours and pseudotumours described in Chapters V—VII comprise totally about 14 per cent of the material The remaining tumours (altogether about 15 per cent) are distributed among the types accounted for in Chapters VIII—XIV, all of which were found by the follow up study to exhibit definite malignancy in the form of metastases and mortality in the tumour disease

Before re classification the parotid tumours were denoted as benign semi malignant or malignant By means of the clinical follow up study they could be divided into benign and malignant respectively The results of this re-classification from the point of view of malignancy can be seen in Table 27

Table 27 Re classification of the material with respect to malignancy

No of tumours	Malignancy Primary	After re classification	No of tumours
378	Benign	Benign	367
		Malignant	11
315	Semi malignant	Benign	286
		Malignant	29
109	Malignant	Benign	12
		Malignant	97
802			802

It can be inferred from Table 27 that, in the primary classification, both the benign and malignant tumours were to a great extent evaluated correctly with respect to malignancy Thus, of the 378 tumours primarily denoted as benign, only 11 (about 3 per cent) proved to be malignant Of the 109 primarily denoted as malignant, 12 (about 10 per cent) proved to be benign

Most of the tumours primarily denoted as benign and found to be malignant were mucoepidermoid carcinomas Most of those originally denoted as malignant and found to be benign were mixed tumours From the point of view of malignancy, the most important result of the re classification is the division of the large "semi malignant" group, comprising 315 cases, into a benign group containing 286 tumours (about 90 per cent) and a malignant group containing 29 (about 10 per cent)

As already mentioned, the tumours primarily diagnosed as semi malignant and found to be benign consisted chiefly of mixed tumours, whereas those which proved to be malignant consisted mainly of mucoepidermoid carcinoma, adenoid cystic carcinoma and acinic cell carcinoma If the tumours denoted in Table 27, after re-classification, as benign and malignant, respectively, are collected into a benign and a malignant group, it is found that the former group contains 665 tumours (82 9 per cent) and the latter 137 (17 1 per cent) How the tumours in these two groups were evaluated with respect to malignancy before re classification is seen in Table 28

Table 28 shows that 367 of the 665 benign tumours (about 55 per cent) were initially denoted as benign, whereas 286 (about 43 per cent) were denoted as semi malignant and 12 (about 2 per cent) as malignant Of the 137 malignant tumours, 97 (just over 70 per cent) were primarily diagnosed as malignant, 11 (about 8 per cent) as benign and 29 (about 21 per cent) as semi malignant

The calculated 5-year survival rate is based on the annual mortality in the tumour disease and as stated earlier, was used in evaluating the malignancy of the various types of malignant tumour in the material To facilitate a comparison between the

Table 28 Present and primary evaluat on of the material with respe t t ma

No of tumours	Malignancy After re-classification	Primary	N of t n rs
665	Benign	Ben gn	36
		Semi mal gnant	28
		Mal gnant	12
137	Malignant	Ben gn	11
		Semi mal gnant	29
		Mal gnant	97
802			802

grade of malignancy of these tumours described in Chapter IV and Chapters VIII—XIV they have been assembled in tabular form (Table 29

In addition to the types of malignant tumour listed in this table the material contains another 6 patients with malignant tumours One had a squamous cell carcinoma 3 had fibrosarcoma and in 2 cases a melanoma malignum was present (probably metastases *cf* p 8?)

It is evident from Table 29 that the highly differentiated form of mucoepidermoid carcinoma in particular was of low grade malignancy Since in the present investigation both metastases and death were demonstrable the highly differentiated form must nevertheless be regarded as definitely malignant Consequently it must be incorrect to denote it as benign (*e g* Stewart *et al* 1945 Marcial Rojas & Sommers 1954), or as semi malignant (*e g* Rauch 1959 Glaser 1962 Hellner 1962 Morehead 1962)

The poorly differentiated form of mucoepidermoid carcinoma showed the lowest survival rate but the group is too small to permit any reliable conclusions

As a rule adenoid cystic carcinoma is still denoted as a semi malignant type of tumour (*e g* Rauch Hellner Glaser Morehead) However in the present investigation it proved to be a clearly malignant tumour of moderate malignancy

Acinic cell carcinoma was found despite its innocent histological picture to be a malignant type of tumour with metastases and death in the tumour disease The 5 year survival rate recorded in Table 29 indicates that acinic cell carcinoma is of low grade malignancy

As can be inferred from Table 29 trabecular adenocarcinoma and solid anaplastic adenocarcinoma had a considerably lower survival rate than the highly differentiated form of mucoepidermoid carcinoma adenoid cystic carcinoma and acinic-cell carcinoma Consequently these two types of tumour together with the poorly differentiated form of mucoepidermoid carcinoma and the malignant mixed tumours must be regarded as highly malignant in comparison to other types

If all the malignant types of tumour in the material with the exception of the malignant mixed tumours are collected into a single group it comprises about 15

Table 29 Different types of malignant tumour calculated 5-year survival rate corrected for deaths in intercurrent diseases

Diagnosis	No of cases followed-up	Died of inter-current disease	5 year survival Total	Calculated %
Malignant mixed tumour	9	2	3	56
Mucoepidermoid carcinoma				86
Highly differentiated	18	3	14	94
Poorly differentiated	3	0	1	33
Adenoid cystic carcinoma	15	0	13	87
Acinic-cell carcinoma	21	2	17	90
Mucus producing adenopapillary carcinoma	7	0	5	71
Trabecular adenocarcinoma	4	0	2	50
Solid anaplastic adenocarcinoma	7	0	4	57

per cent of the whole material The calculated 5 year survival rate for the whole group, after correction for the mortality in intercurrent diseases, is 79 7 per cent That the calculated 5-year survival rate is as high as 79 7 per cent in this collective group of purely malignant tumour types is due to the fact that the highly malignant types — i e, those with the lowest survival rate — comprise a relatively small number of cases Thus the present investigation has shown that 137 of 802 parotid tumours (17 1 per cent) were malignant, but only a small number (51 tumours) were denoted as highly malignant according to the aforegoing grouping The remaining 665 tumours (82 9 per cent) are shown to be benign This implies that, in general the prognosis is relatively good in the presence of a parotid tumour

There was a history of pain in the tumour region in only 43 of the 802 patients in the series It was recorded in 34 (5 1 per cent) of 665 patients with a benign tumour and in 9 (6 5 per cent) of 137 with a malignant tumour No significant difference was present between benign and malignant tumours in this respect (χ^2 = 0 47) No definite conclusions can therefore be drawn from this purely subjective symptom Thus pain cannot be used as a criterion of the malignancy of a parotid tumour

Spontaneous paralysis of the facial nerve is extremely rare in parotid tumours This explains the scarcity of statements in the literature regarding the prognostic conclusions that can be drawn from its occurrence Despite this, spontaneous paralysis of the facial nerve is generally considered to indicate that a parotid tumour is malignant

In the present series persistent paralysis of the facial nerve occurred spontaneously in 12 of the 515 patients followed up for > 5 years In another 3 cases there was a

Table 30 Survival time after onset of spontaneous paralysis of the facial nerve 12 patients with tumours of the parotid gland

No of patients	Survival time years
3	< 1
3	1–2
2	2–3
3	3–4
1	4–5
0	> 5

functional impairment of the nerve, which was fairly rapidly transient, particularly in the 2 cases in which it appeared in connexion with irradiation therapy In one of them the diagnosis was benign mixed tumour and in the other papillary cystadenolymphoma Transient spontaneous paralysis of the facial nerve in association with irradiation therapy has been reported earlier by Frazell (1954), among others The third patient with transient spontaneous facial nerve paralysis in my series was a pregnant woman with a benign mixed tumour, paralysis appeared 2 days before parturition Such paralysis in connexion with pregnancy has been described by Miehlke (1960)

In the 12 patients in whom persistent paralysis of the facial nerve developed spontaneously, the tumour had an exceedingly severe prognosis, irrespective of treatment All the patients were given some form of irradiation therapy Although parotidectomy was performed in 9 of the 12 cases, the prognosis was hopeless This can be inferred from Table 30, which shows the length of survival after the onset of spontaneous paralysis of the facial nerve in these 12 patients

It can be seen that all 12 patients died of the tumour disease within 5 years of the onset of paralysis

As already stated, parotidectomy was performed in 9 of these cases, in 3 of them, total parotidectomy with sacrifice of the facial nerve was done The extremely severe prognosis, despite this measure indicates that a tumour which has invaded the facial nerve is difficult to control therapeutically possibly because metastases may already exist

In all 12 patients now under discussion the tumour was found to have such histological structures that it was classified as one of the types of malignant tumour described Totally 90 patients with tumours distributed among the different types of malignant tumour were followed up for > 5 years during the observation period, 18 of them died of the tumour disease Persistent paralysis of the facial nerve developed spontaneously in 12 of the 18 The incidence of tumours associated with such paralysis in the different types of malignant tumour is shown in Table 31

The present investigation affords evidence that spontaneous paralysis of the facial nerve is a criterion of an exceedingly poor prognosis Consequently a highly malignant type of tumour should be associated with a higher incidence of such

Table 31 Spontaneous paralysis of the facial nerve distribution in different types of malignant parotid tumour

Diagnosis	No of cases followed up	Spontaneous facial nerve paralysis No	%
Malignant mixed tumour	9	2	22
Mucoepidermoid carcinoma			
Highly differentiated	18	0	0
Poorly differentiated	3	1	33
Adenoid cystic carcinoma	15	2	13
Acinic cell carcinoma	21	2	10
Mucus producing adenopapillary carcinoma	7	2	29
Trabecular adenocarcinoma	4	1	25
Solid anaplastic adenocarcinoma	7	2	29
Misc malignant tumours	6	0	0
Total	90	12	13

paralysis than a type of low-grade malignancy The incidence figures given in Table 31 indicate that this is, in fact, the case Thus, in the highly differentiated form of mucoepidermoid carcinoma — as in all types of benign tumour — persistent spontaneous paralysis of the facial nerve was not demonstrable in any case The incidence of persistent spontaneous paralysis of the facial nerve in the different types of malignant tumour substantiates the evaluation of the malignancy, based on the calculated 5 year survival rate (Table 29)

General Summary

It is pointed out that the uncertainty which exists regarding the classification of tumours of the parotid gland is illustrated by the fact that the term semi-malignancy is widely used in connexion with them. This applies particularly to the group of mixed tumours. Since this group of tumours has been difficult to define histologically, it has also been difficult to evaluate from the point of view of malignancy. Nowadays the whole mixed tumour group is often denoted, together with adenoid cystic carcinoma and the highly differentiated form of mucoepidermoid carcinoma, as semi-malignant. This implies that in many classifications no less than about 75 per cent of all parotid tumours are denoted as semi-malignant.

The main object of the present investigation is to test the justification of the term semi-malignancy and to ascertain whether histologically delimited types of parotid tumours can be classified as definitely benign or malignant.

An analysis is therefore made of 864 tumours of the parotid gland involving 802 patients operated on at the Department of Otolaryngology, Karolinska Sjukhuset, in 1950—1962.

A histological re-examination is made of the whole tumour material. It is then re-classified according to such principles that the various types of tumour are histologically clearly defined and well delimited.

After re-classification, the clinical course of the different tumour types is analyzed in a series of 515 patients followed up for > 5 years after operation.

The malignancy of the tumours is evaluated by a study of the correlation between the histological and clinical features of the different types.

The correlation study shows that the histological features generally used as criteria of the semi-malignancy of mixed tumours — *e.g.* high cellularity, dominance of the epithelial component, cylindromatous structures, multiple foci and penetration of the capsule or incomplete encapsulation — are not associated with any malignancy. This implies that the concept of semi-malignancy in mixed tumours lacks justification.

The mixed tumour group, which comprises just over 2/3 of all tumours in the present series, can therefore be divided into a benign group containing about 98 per cent and a malignant group containing about 2 per cent.

Earlier > 50 per cent of mixed tumours were denoted as semi-malignant, which meant that the patients had to undergo life-long regular follow-up examinations. The present investigation shows that these examinations are unnecessary.

The other types of tumour in the material can be specified as benign and malignant respectively through the study of the correlation between histological and clinical features.

Table 31 Spontaneous paralysis of the facial nerve distribution in different types of malignant parotid tumour

Diagnosis		No of cases followed up	Spontaneous facial nerve paralysis No	%
Malignant mixed tumour		9	2	22
Mucoepidermoid carcinoma				
Highly differentiated		18	0	0
Poorly differentiated		3	1	33
Adenoid cysti carcinoma		15	2	13
Acinic cell carcinoma		21	2	10
Mucus producing adenopapillary carcinoma		7	2	29
Trabecular adenocarcinoma		4	1	25
Solid anaplast c adenocarcinoma		7	2	29
Misc malignant tumours		6	0	0
	Total	90	12	13

paralysis than a type of low grade malignancy The incidence figures given in Table 31 indicate that this is, in fact, the case Thus, in the highly differentiated form of mucoepidermoid carcinoma — as in all types of benign tumour — persistent spontaneous paralysis of the facial nerve was not demonstrable in any case The incidence of persistent spontaneous paralysis of the facial nerve in the different types of malignant tumour substantiates the evaluation of the malignancy, based on the calculated 5 year survival rate (Table 29)

Zusammenfassung

Es wird darauf hingewiesen, dass die Unsicherheit in der Klassifizierung von Tumoren der glandula parotis schon in der haufigen Anwendung der Bezeichnung „semimalign" zu Tage tritt Dies gilt besonders fur Mischtumoren Da diese Gruppe von Tumoren nur mit Schwierigkeit histologisch definiert werden kann ist es auch schwer, den Grad der Malignitat zu beurteilen Heutzutage wird oft die ganze Gruppe der Mischtumoren wie auch das adenoid-zystische Karzinom und die hoch-differentierte Form des muko-epidermoiden Karzinomes als semi malign bezeichnet Daraus folgt, dass in vielen Klassifizierungen nicht weniger als etwa 75 % aller Parotistumoren als semimalign bezeichnet werden

Der Hauptzweck dieser Untersuchung ist, zu prufen, ob der Begriff der Semi malignitat eine Berechtigung hat, und zu entscheiden, ob nicht histologisch klar definierte Typen von Parotistumoren eindeutig als gutartig oder bosartig klassifiziert werden konnen

Hierzu wurden 864 Parotistumoren untersucht die an 802 Patienten in der Hals Nasen-Ohrenklinik des Karolinska Sjukhuset, Stockholm, von 1950—1962 operiert wurden

Das gesamte Geschwulstmaterial wurde histologisch nachuntersucht und nach solchen Gesichtspunkten klassifiziert, dass die verschiedenen Tumortypen histologisch klar definiert und voneinander abgegrenzt werden konnten

Nach dieser Re Klassifizierung wurde der klinische Verlauf der verschiedenen Tumorformen in einer Serie von 515 Patienten analysiert, die wahrend mehr als 5 Jahre nach der Operation kontrolliert wurden

Die Malignitat der Geschwulste wurde durch Untersuchung des Zusammenhanges zwischen histologischer Struktur und klinischem Verlauf der verschiedenen Formen beurteilt

Diese vergleichende Studie von Histologie und Klinik zeigt, dass die allgemeinen histologischen Kriterien der Semimalignitat der Mischtumoren wie z B Zellreichtum, Dominanz der epithelialen Komponente, zylindromatose Strukturen multiple Foci, Durchbruch der Kapsel resp Unvollstandigkeit der Kapsel in keinem kausalen Zusammenhang mit der Malignitat einer Geschwulst stehen

Der Begriff der Semimalignitat wird daher bei den Mischtumoren abgelehnt

Die Gruppe der Mischtumoren die gut 2/3 aller Geschwülste dieser Reihe umfasst, kann deswegen in eine benigne Gruppe von etwa 98 % und eine maligne Gruppe von etwa 2 % unterteilt werden

Fruher wurden mehr als 50 % der Mischtumoren als semimalign bezeichnet was fur den Patienten lebenslange regelmassige Nachuntersuchungen mit sich fuhrte Die gegenwartige Untersuchung zeigt dass diese Nachuntersuchungen nicht notig sind

Die übrigen Geschwulstformen in dem bearbeiteten Material können durch das Studium der Korrelation zwischen histologischer Struktur und klinischem Verlauf als benign oder malign bezeichnet werden

Auf der Basis der kalkulierten Fünfjahres Überlebensrate wurde nach Korrektion für interkurrente Todesfälle der Malignitätsgrad der verschiedenen bösartigen Tumorgruppen miteinander verglichen

Es kann festgestellt werden dass die hoch differentierte Form des muko epidermoiden Karzinomes das adenoid zystische Karzinom und das acinic cell Karzinom von geringerer Malignität sind als die malignen Mischtumoren das wenig differentierte muko epidermoide Karzinom das trabekulierte Adenokarzinom und das solide anaplastische Adenokarzinom

Die hoch malignen Formen d h jene mit niedrigster Überlebensrate umfassen eine verhältnismässig geringe Anzahl von Fällen In dieser Untersuchung wurden 137 von 802 Parotistumoren (17 1 %) als bösartig klassifiziert aber nur 51 dieser Fälle (6 4 %) wurden als hoch malign bezeichnet Der Rest von 665 Tumoren (82 9 %) wurde als gutartig klassifiziert

Es wurde auch gefunden dass Schmerzen im Bereich des Tumors nicht als Kriterium für Malignität angesehen werden können

Diese Untersuchung zeigt auch dass eine spontane und persistierende Paralyse des nervus facialis das Zeichen einer äusserst schlechten Prognose ist Das Vorkommen einer Facialisparese dieser Art war bei hoch malignen Geschwulsten häufiger als bei Tumoren von geringerer Malignität Unabhängig von der Behandlung starben alle Patienten mit spontaner persistierender Paralyse des nervus facialis innerhalb von 5 Jahren nach dem Auftreten der Nervenlähmung

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Acta

OTO-LARYNGOLOGICA

S U P P L E M E N T U M 192

INTERNATIONAL VESTIBULAR SYMPOSIUM
UPPSALA 1963
IN MEMORY OF ROBERT BÁRÁNY

ACTA OTO-LARYNGOLOGICA · KARLAVÄGEN 41, STOCKHOLM Ö

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P R O C E E D I N G S O F

INTERNATIONAL VESTIBULAR SYMPOSIUM UPPSALA 1963 IN MEMORY OF ROBERT BÁRÁNY

Published by

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UPPSALA 1964

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UPPSALA 1964

PROGRAMME OF THE SYMPOSIUM

The proceedings were held in the auditorium of the Department of Otolaryngology, University Hospital, Uppsala.

WEDNESDAY, MAY 29TH, 1963

THE RELATION BETWEEN ANATOMY AND PHYSIOLOGY OF THE VESTIBULAR SYSTEM

Opening of the Symposium.

Moderators:
A. Brodal, Oslo, C. S. Hallpike, London, and F. Crabbé, Brussels.

Central Vestibular Pathways and Function

Lecturers:

A. Brodal, Oslo	Anatomical organization and fiber connections of the vestibular nuclei.
C. Fernández, Chicago	Experimental cerebellar lesion and its effect on vestibular function.
G. Aschan, G. Grant and L. Ekvall, Uppsala	Nystagmus following stimulation of the central vestibular pathways using permanently implanted electrodes
G Aschan, *G. Grant* and L. Ekvall, Uppsala	Nystagmus caused by localized cerebellar lesions.

Peripheral Vestibular Function

Lecturers

J. Wersall, Stockholm	Physiological aspects of the structure of the vestibular end organs.
L. Gleisner and *N G Henriksson*, Lund	The activity in the vestibular nerve of the frog.
M R Dix and *C S. Hallpike, London*	Observations upon the neurological mechanism of spontaneous nystagmus in subjects with unilateral tumors of the VIII nerve.

Discussion

(All participants of the Symposium were invited to take part in the discussion)

PRESENT PROBLEMS IN MENIÈRE'S DISEASE

Moderators:

J. R. Lindsay, Chicago, T. Cawthorne, London, and M. Arslan, Padua.

Lecturers:

T. Cawthorne, London	Diagnosis and surgical treatment of Menière's disease.
L. B. W. Jongkees, Amsterdam	Medical treatment of Menière's disease
T. Hasegawa, Osaka	Treatment of Menière's disease by intravenous injection of sodium bicarbonate.
L. Holmgren, Stockholm	Hearing tests in Menière's disease.
M. Arslan, Padua	The effect of ultrasound on the inner ear—experimental and clinical observations. Film: Experimental experience on Menière's disease.
J. Angell James, Bristol	The physical and biological properties of ultra-sound and clinical experience.
A. Sjöberg, Uppsala	Clinical experience with a new Swedish ultrasonic apparatus.
J. *Stahle* and R. Sahl, Uppsala	Electronystagmography in Menière's disease before, during and after ultrasonic irradiation

Discussion

R. Mittermaier, Frankfurt a. M.	Positional nystagmus in Menière's disease.
L. B. W. Jongkees, Amsterdam	The caloric test in Menière's disease.
M. Portmann, Bordeaux	Surgical treatment of Menière's disease.
P. Frenckner, Stockholm	Surgical treatment of Menière's disease.
D. Gordon, London	Studies in the measurements of ultrasonic energy and its effect on nerve tissue.
G. A. Dalton, Birmingham	Methods and results of experimental application of ultrasonics to the animal labyrinth
J. W. S. Lundahl, London	Ultrasonic treatment of Menière's disease
J. G. Waltner, New York	Ultrasonic treatment of Menière's disease

J Stahle, Uppsala	Animal experiments on the effect of ultrasound
D E Hughes and J T Y Chou, Oxford	The biochemistry of the inner ear with special reference to the effect of ultrasound

Discussion

(All participants of the Symposium were invited to take part in the discussion)

FRIDAY MAY 31ST 1963

ACTIVITIES AT THE UNIVERSITY

Gathering at the University

Meeting of the Barany Society

Conferring of the Barany Jubilee Medal on Profe sor Alf Brodal

Awarding of Doctors' Degrees at the University and Honorary Doctorates to Professor Michele Arslan, Mr Terence E Cawthorne, F R C S , and Professor John R Lindsay

Traditional Doctors' Banquet at Uppsala Castle with ladies

SATURDAY JUN T 1963

A Sjoberg – J Stahle – S Johnson

Ultrasonic irradiation Clinical demonstrat the operating theatres of the Department of Otolaryngology

INTRODUCTORY ADDRESS

RECTOR MAGNIFICUS PROFESSOR TORGNY SEGERSTEDT
University of Uppsala

On behalf of the University of Uppsala I have the great pleasure and privilege of welcoming all of you to this international symposium in memory of Robert Bárány. Robert Bárány was one of the famous professors of this university. But at the same time as we are proud of the research work he carried out here in Uppsala, we are fully aware of the fact that his stimulating and fruitful work was done because of his international background. This university is now more than 485 years old and I think we can say that its weak periods have occurred at those times when it has tried to isolate itself in a kind of national self-sufficiency.

In our days we know that national isolation in science and research is more dangerous than ever; we must exchange scientific results across the national border lines and it is our duty to disseminate them and to make them available to everyone. In this changing world the importance of science is rapidly increasing and I believe that all of us should feel the international responsibility in the capacity of scientists and scholars. The future of mankind is essentially depending on our way of using the scientific results.

We are fully aware of the great importance of international contacts and we believe that gatherings of this kind give the best opportunity of meeting friends and colleagues and of exchanging views. For this reason it is a great pleasure and a source of satisfaction to the University of Uppsala to be the sponsor of this symposium. We are happy and proud to see you here today and I give everyone of you a hearty welcome and do hope that your stay in our university town will be interesting and profitable to all of you.

And with these words I hereby declare this International Vestibular Symposium opened.

WORDS OF WELCOME TO THE DELEGATES

PROFESSOR ARNE SJOBERG HEAD OF THE DEPARTMENT
OF OTOLARYNGOLOGY
Uppsala Sweden

We are very pleased that our Rector Magnificus has been able to come here today to open this Symposium It is due to the generosity of the University and its Faculty of Medicine that we have been able to hold this gathering

I would also like to extend you a warm personal welcome to the Otolaryngological Clinic and this Symposium which is devoted to the memory of Robert Barany a great pioneer in the field of research that unites us all — the vestibular apparatus in its widest aspects

Space research represents a characteristic symbol of this century and for this reason increased knowledge of the function and disturbances of the balance apparatus in its entirety will probably become of even greater importance in the future

We hope that this Symposium will not only enable us to extend our international contacts and bonds of friendship but also contribute to a more definite neuro physiological and neuro anatomical basis both for oto neurology and for experimental and clinical vestibular research — all for the well being of our patients

We sincerely hope that both you and your ladies will enjoy your visit to this ancient university town which after a long hard northern winter has now its finest attire for the springtime

Heartily welcome

CONFERRING OF THE BÁRÁNY JUBILEE MEDAL ON PROFESSOR ALF BRODAL, NORWAY

ARNE SJÖBERG
Uppsala, Sweden

Robert Bárány was born in Vienna 1876, but his father was born in Hungary. Bárány himself received his otological training in Vienna under Adam Politzer. In 1915–1916 Bárány was for more than one year a prisoner of war in the town of Merv, far within Russia. One day during this period when he was on his way home in a *drosky* from an ear operation at a civilian hospital, he met with an experience which he said was "the greatest surprise of his life". — He was dramatically stopped at the military headquarters by a Russian soldier who handed him a telegram from the Swedish Ambassador in Petrograd, General Brändström, which announced that he had been awarded the Nobel Prize in medicine for his work on the physiology and pathology of the vestibular apparatus. The following day he was informed that he would soon be released from his captivity, but his immediate feelings of "overwhelming happiness" were soon changed into heavy disappointment. It was not until the 16th of June 1916 that the hour of deliverance struck, and through the intermediation of Prince Charles of Sweden Bárány was exchanged and stood on Swedish soil in Haparanda.

Our Faculty of Medicine succeeded in getting Bárány to come to this country and to the University Hospital of Uppsala in 1917. During that year he was given the title of professor. In 1924 Bárány became honorary doctor of medicine at the Karolinska Institutet in Stockholm. In 1926 he was appointed professor ordinarius in Uppsala.

Under his skilful and imaginative guidance Bárány's Ear clinic soon became an often visited research and training centre of international reputation.

Bárány would have been 60 years old on the 22nd of April 1936, but he died on the 8th of April of that year.

It was intended, on the initiative of the great organizer and founder of the Swedish otology, Gunnar Holmgren, that after a world wide collection the sum received should be presented to Bárány on his birthday. But in 1937, the year after Bárány's death, Gunnar Holmgren presented the basic sum, which had become the Robert Bárány Jubilee fund, to this University. It was stated in the regulations that every fifth year a medal, struck of gold, should be conferred by the Faculty of Medicine on that author, regardless of nationality or race, who, during the last five year period, had published the most valuable work concerning the vestibular apparatus, in the widest sense of the term.

Presentation of the medal will be done according to the suggestion to the



Fig. 1

Faculty of a committee consisting of the professor of otolaryngology (chairman), the professor of neurology and the professor of ophthalmology.

The medal was designed by Professor Erik Lindberg, and all participants in the International Symposium have seen its reproduction in our programme, with Bárány's likeness on the front cover, and the wreath on the back with the inscription: *Excellenti auris vestibuli investigatori ordo medicorum upsaliensis* (Fig. 1).

The medal has previously been presented three times, namely in 1948 to Professor Adriaan de Kleyn, Amsterdam, in 1953 to Professor A. A. J. van Egmond, Utrecht, and in 1958 to Mr. C. S. Hallpike, F.R.C.S., London.

This year the Faculty of Medicine has decided that the Bárány Medal should be awarded to the professor of anatomy at the University of Oslo, Alf Brodal.

Brodal was born in 1910 and has been a professor since 1950.

Even if today, as Brodal himself once so aptly remarked, we still know deplorably little about how the brain, our finest and most important organic system, works, our knowledge has, however, increased considerably as a result of the careful brain research which Brodal and the Oslo school [illegible] shown in the form of elegant results.

[illegible] the foundation of his knowledge of the human nervous system [illegible] at the neurological clinic in Oslo under the leadership [illegible] for the prospective neuro-anatomist this was a necessary [illegible]ing



Fig 2

Soon afterwards Brodal joined the neuro anatomical research group at the Anatomical Institute in Oslo led by Jan Jensen

Brodal however soon became an independent researcher and after studies in Oxford the U S A and Scandinavia he became well versed not only in neuro anatomical and neuro pathological research but also in neuro physiological problems

He nowadays is something of a pioneer His work has been of the greatest importance even to the clinical neurologist

Brodal s laboratory in Oslo has become one of the leading centres in the international field of neuro anatomy and he receives there numerous visitors from all over the world He has also succeeded in inspiring a number of young Norwegian and foreign workers Brodal is not only a very prominent researcher but is also a skilful teacher who has published several monographs and excellent textbooks in applied neuro anatomy and neuro physiology

His scientific production in modern brain research is thus considerable and represents a gigantic contribution of work even from a purely experimental technical aspect He uses mainly classic routes in the field of neuro anatomy

At an early date Brodal and his group has studied the cerebellum and the medulla oblongata But his main interest is associated with the vestibular nerve and the organization and physiological mode of function of its nuclear regions

In collaboration with prosektor Wahlberg and the professor of physiology in Pisa Pompeiano Brodal has performed section experiments and lesions

MEETING OF THE BÁRÁNY SOCIETY AT THE UNIVERSITY OF UPPSALA

In order to honour the memory of Professor Robert Bárány and to increase the contacts between vestibularis investigators and also to stimulate the oto-neurological scientific research work Professor C. O. Nylén suggested in 1958 the creation of an international society named after Robert Bárány. When Dr C. S. Hallpike was awarded the Bárány golden medal in 1958 the subject was discussed. As a result the Bárány Society was founded at a business meeting in Padua on the 1st of September, 1960, and C. O. Nylén was elected president of the new society.

The next informal meeting of the Bárány Society was held in Paris on the 2[illegible]th of July in connection with the International Oto-Laryngological congress. In the absence of the ordinary president, Professor Nylén, and with the approval of the members present, Professor G. Dohlman presided at this meeting.

At this meeting in Paris the members of the Society had been advised through communications previously circulated that the subject to discuss was the future structure and working conditions of the Society. Several young colleagues interested in vestibular problems were anxious to establish an international organization for the arrangement of meetings and the publication of the results of vestibular research. It was felt that this could be done by reorganizing the existing Bárány Society and allowing a greater number of members to be elected. The main object would be a working society, organizing symposia and meetings.

Discussions were unanimously in favour of a motion to increase the number of members of the Bárány Society. It was further decided to elect a vice-president and a secretary, who were to be entrusted with the task of making the Society a working organization. Professor A. Sjöberg was elected vice-president and Dr J. Stahle secretary.

Each of the present member countries was advised to select two members who would act as a committee to propose candidates for membership. Such candidates were to be elected only if their scientific publications were regarded as being of acceptable standard.

The motion was passed that the present members of the Bárány Society should be known as *Charter Members*, those over seventy as *Honorary Members*, and those newly elected as *Regular Members*.

The *subscription* to be collected by the treasurer was fixed at *one pound (£ 1)* per annum to cover the expenses of the Society.

[illegible] presentation of the Bárány Medal in Uppsala during the last
[illegible] year should however if possible be combined with
[illegible] Uppsala
[illegible] Sjöberg moved that the first working

meeting of the reorganized Barany Society should be held in Uppsala and invited the members to the meeting at the end of May, 1963

As the Barany Society itself does not have the status to finance an international meeting the University of Uppsala and its Faculty of Medicine engaged to sponsor an International Vestibular Symposium in Uppsala May 29 – June 1 1963 The University of Uppsala had the honour and pleasure to invite all members of the Barany Society to this Symposium

In connection with the Symposium in Uppsala the Barany Society had a business meeting At this meeting new members were elected and the future working conditions of the Society were discussed It was decided that the presidium of the Society should have a *co ordination committee of members from different countries to be in charge of international contacts Hallpike Lindsay M Portmann Jongkees Fren el and Ledoux were elected members of this committee*

The president Professor C O Nylen wanted to resign due to his age and health Professor G Dohlman suggested *Professor Nylen* to be elected *Honorary President* and this was accepted with acclamation *Professor Arne Sjoberg was elected new president* The other two members elected to the board were *Assistant Professor Gunnar Aschan secretary and Assistant Professor Jan Stahle treasurer*

To make it easier to arrange meetings in different parts of the world it was suggested and accepted that the vice president should be elected temporarily in such a way that a member of the Society in that country in which the Society planned to hold a meeting should be elected for each meeting

The board must always maintain a strict supervision in order to keep the programmes at every meeting on a very high scientific level

The Honorary President C O Nylen closed the meeting and presented the Barany Society with a gavel

ACKNOWLEDGMENTS

The formal presentation of the Barany Jubilee Medal in Uppsala every fifth year should be combined with a festival working meeting As the Barany Society itself does not have the status to finance an international meeting the University of Uppsala due to favourable interest of Rector Magnificus became sponsor and the Faculty of Medicine arranged this International Vestibular Symposium at the Department of Otolaryngology University Hospital

The publication of the Proceedings of this Symposium has been made possible through financial support of the Swedish Medical Research Council and the Jubilee Foundation of the Insurance Company Skandia Stockholm

ANATOMICAL OBSERVATIONS ON THE VESTIBULAR NUCLEI, WITH SPECIAL REFERENCE TO THEIR RELATIONS TO THE SPINAL CORD AND THE CEREBELLUM

ALF BRODAL
Oslo, Norway

From the Anatomical Institute, University of Oslo, Norway

Introduction

Recent neurological research furnishes us with an ever increasing number of data which bear witness of the intriguingly complex organization of the nervous system. Every new step forward in our exploration of the patterns of neuronal organization brings to light new details, making the picture richer and more highly differentiated than we assumed it to be only a few years ago. Concerning structure this holds true for the minutest features in the anatomy of the nerve cells, such as the places of synaptic contact between neurons, but it is equally true with regard to the organization of cells into groups or nuclei and their mutual connections. Obviously such anatomical dissimilarities must be related to functional differences, and even if satisfactory correlations of structural and functional features cannot always be made, modern neurophysiological research tells the same story of an extreme degree of differentiation in the organization of the nervous system.

These general considerations are certainly valid for the vestibular system, the subject of this symposium. It is therefore impossible in a short lecture to give a complete account of our present day knowledge of the anatomy of those parts of the central nervous system which are more or less directly related to vestibular function. Charged with the task of doing so, I will have to select certain features for consideration and delete others. I have chosen to deal largely with two aspects, the relations of the vestibular nuclei to the spinal cord and to the cerebellum. Readers interested in the subject will find further data in our original publications, in two other reviews by the author (Brodal, 1960, 1964) and in a recent monograph (Brodal, Pompeiano & Walberg, 1962). Some of the data to be presented have not yet been published. My presentation will be centred around the results of experimental research in the cat, carried out in collaboration with a number of colleagues [illegible] the Anatomical Institute, University of Oslo. References to the literature [illegible] limited to a minimum, since complete references are found in our [illegible]

[illegible] the relations of the vestibular nuclei to the spinal cord [illegible] appropriate to consider the normal topography [illegible] vestibular nuclei. Furthermore some major points

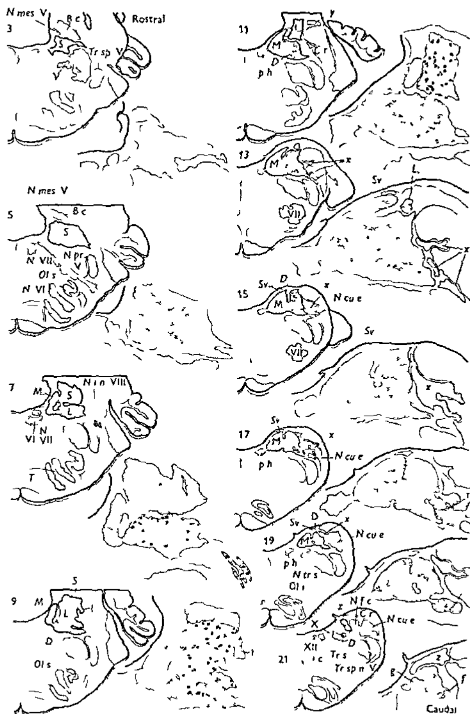


Fig. 1. A series of equally spaced camera lucida drawings of transverse sections through the brain stem of the cat to show the topography and (below to the right of each drawing) the chief cytoarchitectural features of the vestibular nuclei. The rings in the descending nucleus represent the longitudinally running fibre bundles within this. From Brodal & Pompeiano (1957*a*).

in their fibre connections should be mentioned. It will be practical to do this with reference to the nucleus of Deiters, since this is a part of the nuclear complex which is connected with the spinal cord as well as the cerebellum.

The Vestibular Nuclear Complex

A closer analysis of the normal architecture of the vestibular nuclei shows that this nuclear complex is composed of more cell groups than the four

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List of abbreviations employed in Figures 1, 5, 8, 9, 10, 15 and 16

B.c. Brachium conjunctivum
C.r. Corpus restiforme
D Descending (spinal) vestibular nucleus
f Cell group f in descending vestibular nucleus
Fl. Flocculus
g Group rich in neuroglia cells, caudal to the caudal end of the medial vestibular nucleus
I.c. Nucleus intercalatus (Staderini)
L Lateral vestibular nucleus (Deiters)
l Small celled lateral group of lateral nucleus
M Medial (triangular or dorsal) vestibular nucleus
N.cu.e. Nucleus cuneatus externus
N.d. Nucleus dentatus
N.f. Nucleus fastigii
N.f.c. Nucleus funiculi cuneati
N.f.g. Nucleus funiculi gracilis
N.i. Nucleus interpositus cerebelli
N.i.a. Nucleus interpositus anterior
N.in.VIII Nucleus interstitialis nervi vestibuli
N.l. Nucleus lateralis (dentatus) cerebelli
N.m. Nucleus medialis (fastigii) cerebelli
N.mes.V Nucleus mesencephalicus n. V
N.sl. N. ... tulus
N.pr.V Nucleus sensibilis principalis n. V
N.p.s. Nucleus parasolitarius
N.tr.s. Nucleus tractus solitarii
N.tr.sp.V Nucleus tractus spinalis nervi V
V, VI, VII, VIII Cranial nerves VI, VII and VIII
Ol.i. Oliva inferior
Ol.s. Oliva superior
p Small celled part of lateral cerebellar nucleus
P.fl.d. and *P.fl.v.* Dorsal and ventral paraflocculus, respectively
p.h. Nucleus praepositus hypoglossi
S Superior vestibular nucleus (Bechterew)
Sv. Cell group probably representing the nucleus supravestibularis
Tr.s. Tractus solitarius
Tr.sp.n.V Tractus spinalis n. V
Uv. Uvula
X, XI, XII, XII Cranial motor nerve nuclei
x ... parasympathetic vagus nucleus
x ... lateral to the descending vestibular nucleus
y ... lateral to the lateral vestibular nucleus (Deiters)
... the caudal part of the descending vestibular nucleus

classical large nuclei, the superior, medial, lateral (or Deiters') and descending (or inferior) Furthermore, each of them is not uniformly structured throughout This is seen from Figure 1, a cytoarchitectonic map of the vestibular nuclei in the cat, prepared on the basis of serial transverse Nissl stained sections (Brodal & Pompeiano, 1957*a*) Thus there are architectonic differences, for example, within the superior nucleus (S) with a crowding of larger cells centrally, in the lateral nucleus (L) with larger and more densely packed giant cells dorsocaudally, while the number of small cells is less in this part than rostroventrally, and within the medial nucleus (M) In the descending nucleus the group f of Meessen & Olszewski (1949), composed of densely packed, relatively large cells (drawings 17 21 in Fig 1), stands out as a special part (see also Fig 2B) The lateral nucleus of Deiters has on its lateral aspects a little group of small cells labelled l (drawing 9 in Fig 1) Of other special groups there is one which we have labelled x (drawings 13 19), interposed between the descending nucleus, the external cuneate nucleus and the restiform body There is the interstitial nucleus of the vestibular nerve of Cajal (drawing 7), a group which we have called y, dorsal to the restiform body (drawing 11) a small group z dorsolateral to the caudal part of the descending nucleus, and finally a group which we, following Meessen & Olszewski (1949) in the rabbit, have labelled the nucleus supravestibularis (Sv in Fig 1)

It has been gratifying to learn in our subsequent studies that subdivisions identified on the basis of their cytoarchitecture betray differences with regard to their fibre connections as well, as will be seen from the following presentation To avoid repetitions it is appropriate to give a brief account of the methods employed in our experimental studies

Experimental Studies of Vestibular Fibre Connections

Most of the classical studies of the fibre connections of the vestibular nuclei were performed with the Marchi method Since this is a method which demonstrates degenerating myelin sheaths it follows that it is incapable of giving information on some important points Unmyelinated fibres will escape recognition, as will the fine terminal arborizations of degenerating fibres since these lack a myelin sheath Terminal boutons will likewise remain unimpregnated These difficulties can be overcome by the use of silver impregnation methods where the axon and its finest ramifications—and often the terminal boutons as well—are impregnated When the distal part of a transected nerve fibre degenerates, it is thus possible by using such methods to identify myelinated as well as unmyelinated fibres The precise sites of ending of transected fibres can be established (see Fig 2B) and their synaptic contacts can be studied (Fig 2A) For example, it can be decided whether the transected fibres end in contact with cells of one type only in a nucleus containing cells of different types

In our studies we have chiefly used two methods, that of Nauta (1957),

in their fibre connections should be mentioned. It will be practical to do this with reference to the nucleus of Deiters, since this is a part of the nuclear complex which is connected with the spinal cord as well as the cerebellum.

The Vestibular Nuclear Complex

A closer analysis of the normal architecture of the vestibular nuclei shows that this nuclear complex is composed of more cell groups than the four

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List of abbreviations employed in Figures 1, 5, 8, 9, 12, 13 and 16

B c Brachium conjunctivum
C r Corpus restiforme
D Descending (spinal) vestibular nucleus
f Cell group f in descending vestibular nucleus
Floc Flocculus
g Group rich in neuroglia cells caudal to the caudal end of the medial vestibular nucleus
i c Nucleus intercalatus (Staderini)
L Lateral vestibular nucleus (Deiters)
l Small celled lateral group of lateral nucleus
M Medial (triangular or dorsal) vestibular nucleus
N cu e Nucleus cuneatus externus
N d Nucleus dentatus
N f Nucleus fastigii
N f c Nucleus funiculi cuneati
N f g Nucleus funiculi gracilis
N i Nucleus interpositus cerebelli
N i a Nucleus interpositus anterior
N i n VIII Nucleus interstitialis nervi vestibuli
N l Nucleus lateralis (dentatus) cerebelli
N m Nucleus medialis (fastigii) cerebelli
N mes V Nucleus mesencephalicus n. V
Nod Nodulus
N pr V Nucleus sensibilis principalis n. V
N p s Nucleus parasolitarius
N tr s Nucleus tractus solitarii
N tr sp V Nucleus tractus spinalis nervi V
V, VI, VII, VIII Cranial nerves VI, VII and VIII
Ol i Oliva inferior
Ol s Oliva superior
p Small celled part of lateral cerebellar nucleus
Pfl d and *Pfl v* Dorsal and ventral paraflocculus, respectively
p h Nucleus praepositus hypoglossi
S Superior vestibular nucleus (Bechterew)
Sv Cell group probably representing the nucleus supravestibularis
Tr s Tractus solitarius
T sp n V Tractus spinalis n. V
U Uvula
V, VI, VII, XII Cranial motor nerve nuclei
r (parasympathetic) vagus nucleus
i x lat ral to the descending vestibular nucleus
y lateral to the lateral vestibular nucleus (Deiters)
h caudal part of the descending vestibular nucleus

vestibular fibres supplying the various subdivisions of the vestibular complex are derived from particular receptive regions in the labyrinth. However, from the studies of Lorente de Nó (1926, 1933, for a discussion see Brodal, Pompeiano & Walberg, 1962) it may be concluded that the fibres to the superior nucleus and possibly the medial nucleus as well are derived from the cristae only. The lateral nucleus of Deiters appears to be supplied, at least chiefly, by fibres from the utricular macula, other fibres from the utricle appear to end in the descending nucleus, which in addition receives fibres from the cristae and the saccular macula.

Although we have no relevant personal observations on these subjects it may be worth mentioning the *connections of the vestibular nuclei with the reticular formation* and the efferent vestibular nerve fibres. There seem to be abundant anatomical possibilities for a collaboration between the vestibular nuclei and the reticular formation, although these connections are not known in detail and are difficult to study experimentally. The *efferent vestibular fibres*, advocated by some early authors, have recently been investigated in some detail by Rasmussen & Gacek (1958) and Gacek (1960) and traced to all subdivisions of the labyrinth. The suggestion of Gacek (1960) that they may be derived from the nucleus of Deiters has recently been confirmed (in the guinea pig) by Rossi & Cortesina (1962) who furthermore found some fibres to come from a particular small cell group which they call the "interposed vestibular nucleus".[1] Finally, there appear to be some efferent fibres from the reticular formation. In contrast to the afferent vestibular fibres, the efferent ones are cholinesterase positive.

It remains to consider the fibre connections linking the vestibular nuclei with the cerebellum and the spinal cord. Of all vestibular nuclei the lateral has the most massive connections of these kinds. Since the nucleus of Deiters, furthermore, is the best example to illustrate some general features in the organization of the vestibular nuclei it will be practical to consider this nucleus in some detail.

The Lateral Vestibular Nucleus of Deiters and its Fibre Connections

According to our (Brodal & Pompeiano, 1957*a*) definition the term "nucleus of Deiters" should be restricted to that part of the vestibular complex which is characterized by the presence of large multipolar (giant) cells,[2] a view held by authorities such as Cajal (1909–11) and Kappers, Huber & Crosby (1936). It should be emphasized, however, as will be seen

[1] This cell group, which was not identified as a particular nucleus in our study (Brodal & Pompeiano, 19[illegible] *a*), according to Rossi & Cortesina (196[illegible]) contains (in the guinea pig) some 1[illegible] [illegible] cells. It is interesting to note that Gacek gives the number of myelinated efferent vestibular fibres in the cat as being about [illegible].

[2] The [illegible] part of the descending nucleus contains some fairly large cells as well, but [illegible] in other respects from the lateral nucleus.

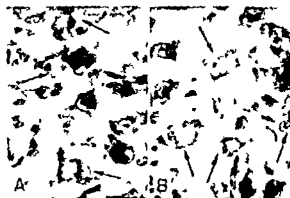


Fig. [illegible]. Photomicrographs of Nissl stained sections through the medial (A) and descending (B) vestibular nucleus of the kitten showing some cells affected with typical retrograde changes (arrows) following cerebellar lesions involving the nodulus and flocculus. ×300. From Brodal & Torvik (1957).

vestibular nuclei appear to be scanty. According to Pompeiano & Walberg (1957) they supply only the medial vestibular nucleus, chiefly dorsally and caudally, and they appear to be derived from the interstitial nucleus of Cajal only.

From a functional point of view the *primary vestibular fibres* are of special interest. When we undertook an experimental analysis of these fibres (Walberg, Bowsher & Brodal, 1958) we were rather surprised to find that they do not supply the entire territory of the classical vestibular nuclei. In the superior nucleus, for example, primary vestibular fibres end only in its central region (Fig. 5), that is the part in which the cells are largest and most densely packed (see Fig. 1, drawing 5). In the same manner, as seen from Figure 5, certain parts of the lateral, the descending and medial nucleus receive primary vestibular fibres while other parts do not. Of the small groups enumerated above, only the interstitial nucleus of Cajal, and, as established later (Brodal & Høivik, 1964), the group x, receive primary vestibular fibres, while groups x and f are free.[1]

A scrutiny of the relevant literature shows that a few previous authors (for references see Walberg, Bowsher & Brodal, 1958; Brodal, Pompeiano & Walberg, 1962) have noted this limited distribution concerning the lateral nucleus of Deiters, but their observations have been forgotten and have not found their way into the textbooks. Our results have subsequently been confirmed by Carpenter (1960).

Our studies do not permit any conclusions as to whether the primary

[1] [illegible] primary vestibular fibres supply only parts of all the four classical vestibular [illegible] whether it is correct to retain the term "vestibular nuclei" as a collec[illegible] [illegible] certain parts of the superior, lateral, medial and descending [illegible]. However, for practical reasons it seems advisable to retain the old [illegible] [illegible] tions are realized.

[illegible]

appears to be agreement that the vestibulospinal tract extends ipsilaterally to the lowest levels of the cord. Furthermore, most authors are of the opinion that the lateral vestibular nucleus is the sole origin of the vestibulospinal tract. When, in spite of this, we decided to investigate the vestibulospinal projection, it was for a particular reason. It has been known for some time that there is in the anterior lobe of the cerebellum a somatotopic localization and that localized stimulations or ablations result in changes in muscular tone and myotatic reflexes in the fore- or hindlimbs, respectively, according to the pattern of localization. This effect has generally been assumed to be mediated via the reticular formation. However, responses on stimulation of the reticular formation betray no somatotopic localization (Sprague & Chambers 1954), and in 1957 we (Torvik and Brodal) found that anatomically there is no somatotopic localization within the reticulospinal projection. The current theory then seemed unlikely (and its untenability was finally demonstrated when it was shown in 1962 by Walberg, Pompeiano, Westrum and Hauglie-Hanssen that the fastigioreticular projection as well is diffusely organized). The question therefore naturally arose whether the vestibular nuclei, known to receive fibres from the cerebellum, might be the link in the brain stem which permit a somatotopically localized transmission of impulses from the anterior lobe of the cerebellum to the cord. This would require the presence of a somatotopic localization in the projection from the lateral vestibular nucleus of Deiters onto the cord.

In our study of the vestibulospinal projection we (Pompeiano & Brodal 1957*a*) used the modified Gudden method, as referred to above. Following sections of the spinal cord in kittens a few days old, retrograde cellular changes in the vestibular nuclei were restricted to the nucleus of Deiters. However, small as well as large cells were affected, i.e. not only large but also small cells send their axons to the cord. Furthermore, the projection is clearly organized in a somatotopic manner, as seen in Figure 6, best in the reconstruction of the nucleus in the sagittal plane in B. The rostroventral part sends its fibres to the cervical cord, the dorsocaudal to the lumbosacral cord, the intervening part to the thoracic cord. One may therefore speak of a neck and forelimb region, a trunk region and a hindlimb region within the lateral vestibular nucleus. This localization has further been confirmed in physiological experiments by Pompeiano (1960) and in degeneration studies following lesions of the nucleus (Nyberg-Hansen & Mascitti 1964). The vestibulospinal projection therefore fulfills the anatomical requirements for being a link in a somatotopically organized pathway from the cerebellum to the cord.

Our findings concerning the vestibulospinal projection strengthened our suspicion that the pathway from the cerebellum to the cord responsible for the localized effects on stimulation of the anterior lobe passes via the nucleus of Deiters. A next step was therefore to analyse the projections of the anterior lobe onto this nucleus. It has been known for a long time that the anterior lobe disposes of two routes to the vestibular nuclei. There is a direct

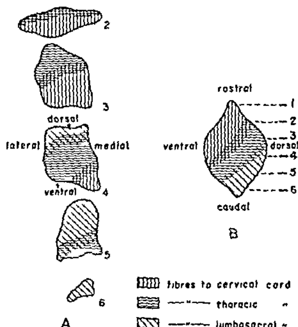


FIG 6 Diagrams to show the somatotopic arrangement of the origin within the lateral vestibular nucleus of fibres passing to different levels of the cord To the left (A) the pattern is shown as seen in transverse sections to the right (B) as it appears when projected on a sagittal reconstruction of the lateral vestibular nucleus From Pompeiano & Brodal (1957a)

one from the cortex to the vestibular nuclei, the other consists of two links of neurons, with a synapse in the fastigial nucleus Although these fibre systems have been studied by several students the question whether they show any somatotopic arrangement does not appear to have been considered Using silver impregnation methods, and by making appropriate, restricted lesions it has been possible to provide an answer to this question It is possible here to give a brief summary of the results only

The organization of the *direct cerebello vestibular pathway* was studied by Walberg & Jansen (1961) Figure 7 shows to the left a summarizing diagram of their findings As will be seen fibres from the forelimb region of the anterior lobe end in the forelimb region of the ipsilateral nucleus of Deiters, and there is a similar correspondence between the hindlimb regions of the two structures (In addition these regions receive a lesser number of fibres from the posterior lobe, as seen in Fig 7) It is, however, striking that the terminations of the direct cerebellovestibular fibres do not cover the entire forelimb and hindlimb regions of the nucleus of Deiters The terminal area is limited to the dorsal half of the nucleus, while its ventral half is free from degeneration The border between the part in receipt of direct cerebellovestibular fibres crosses the border between the fore and hindlimb regions

To the right in Figure 7 is shown a summarizing diagram of our (Walberg, Pompeiano, Brodal & Jansen, 1962) findings concerning the other *cerebellovestibular pathway to the nucleus of Deiters passing via the fastigial nucleus*

Our results in principle confirm and extend the observations of some other workers. We know from previous studies in our laboratory (Jansen & Brodal 1940, 1942) that the projection of the cerebellar cortex onto the intracerebellar nuclei is arranged in a regular pattern (see Fig. 7, to the right), an observation which has recently been confirmed and worked out in greater detail with silver impregnation methods (Walberg and Jansen 1964). It is possible, therefore, to indicate certain parts of the fastigial nucleus as being either fore- or hindlimb regions.

As will be seen from the diagram, fibres from the rostral part of the fastigial nucleus pass to the dorsal half of the ipsilateral nucleus of Deiters (Fig. 7, to the right), that is to the same part which receives fibres directly from the cerebellar vermis (Fig. 7, to the left). This pathway from the anterior lobe via the rostral part of the fastigial nucleus shows a localization in a somatotopic manner throughout. This is the case also for the projection from the posterior lobe vermis, but this takes another route. The cerebellar fibres end in the posterior (caudal) part of the fastigial nucleus, and this sends its fibres to the contralateral vestibular nuclei via the hook bundle. In the nucleus of Deiters these fibres end in its ventral part only, i.e. that part which is not supplied by fibres of the two routes from the anterior lobe.

The anatomically demonstrated somatotopic pattern in the cerebello-vestibular connections has been confirmed physiologically by Pompeiano & Cotti (1959) who recorded potentials from single units in the nucleus of Deiters following stimulation of individual folia of the anterior lobe.[1] The somatotopic localization in the caudal part of the fastigial nucleus has likewise been physiologically confirmed (Pompeiano 196[illegible]).

There is thus clear evidence that there are pathways from the anterior as well as the posterior lobe of the cerebellum which are organized so as to make possible a somatotopically localized transmission of impulses to the nucleus of Deiters, from which another similarly organized pathway, the vestibulospinal tract, carries impulses to particular levels of the cord. The somatotopically localized responses on muscular tone and myotatic reflexes observed on stimulation of the anterior and posterior vermis, therefore, are probably brought about by transmission along this pathway, while the cerebello-fastigio-reticulo-spinal route, although involved in the cerebellar influences on spinal mechanisms, cannot be responsible for the localization of the phenomena.

As was mentioned above, small as well as large cells of the nucleus of Deiters project onto the spinal cord. It is of considerable functional interest that the two types of cells differ with regard to their cerebellar afferents. The large and giant cells are contacted by the direct fibres from the cerebellar cortex (Walberg & Jansen 1961), while the fibres from the fastigial

[1] Whether the effects on the nucleus of Deiters elicited from the anterior lobe are mediated by the direct fibres or via the pathway involving the fastigial nucleus has so far not been decided (for a discussion see Brodal, Pompeiano & Walberg 19[illegible], p. 153 ff.).

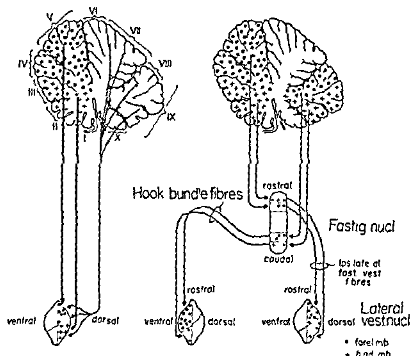


FIG. 7. Diagram illustrating major features in the projections from the cerebellar cortex onto the nucleus of Deiters (to the left) and (to the right) in the projections from the cerebellar cortex onto the fastigial nucleus and from this to the lateral vestibular nuclei. Note that the direct cerebello-vestibular fibres and the projection from the rostral part of the fastigial nucleus end in the dorsal half of the ipsilateral lateral vestibular nucleus, while the fibres from the caudal part of the fastigial nucleus via the hook bundle supply the ventral half of the contralateral lateral vestibular nucleus. Within each of these projections there is a somatotopic localization. Cp. text. From Brodal, Pompeiano & Walberg (1962).

nucleus establish synaptic contact, at least largely, with the small cells (Walberg, Pompeiano, Brodal & Jansen, 1962).

The lateral vestibular nucleus of Deiters is well known to exert a marked influence on myotatic reflexes and muscular tone and especially to facilitate extensor motoneurons, activating α as well as γ neurons of the cord (Andersson & Gernandt, 1956). It is tempting to hypothesize that the different synaptic relationships of the two kinds of cerebellovestibular pathways, on small and large cells, respectively, may bear some relation to the role played by the cerebellum in its linking of influences on α and γ neurons in the cord (Granit, Holmgren & Merton, 1955).

In view of the action of the lateral vestibular nucleus on the cord it is of interest to know *where and how the vestibulospinal fibres end in the spinal grey matter*. Different opinions have been held on this subject by previous authors and information is still insufficient. For these reasons, Nyberg-Hansen & Mascitti (1964) in our laboratory have undertaken a study of the problem using silver impregnation methods. Following stereotactic electrolytic lesions of the lateral vestibular nucleus they mapped the sites of termination of the vestibulospinal fibres with regard to the cytoarchitectonic

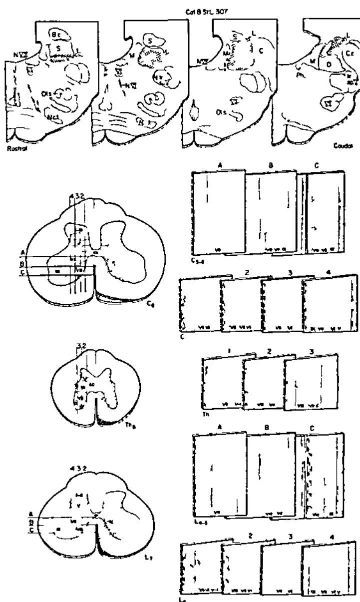


Fig 8 Diagrammatic representation of the course and site of termination (dots) of vestibulospinal fibres in the cat as determined experimentally Above a diagram of the lesion confined to the lateral vestibular nucleus The Roman numerals refer to Rexed s (1952 1954) zones Note absence of termination in lamina IX harbouring the motoneurons Abbreviations as in Figure 1 From Nyberg Hansen & Mascitti (1964)

laminae of the spinal grey matter, established by Rexed (1952 1954) The fibres were found to end in laminae VII and VIII only (Fig 8) It thus appears that in the cat at least vestibulospinal fibres do not establish synaptic contact neither with large motoneurons nor with γ neurons since these, according to the physiological observations of Eccles Eccles Iggo & Lund

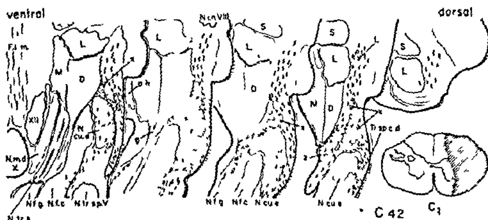


FIG. 9. A diagram of a series of horizontal sections showing the distribution of terminal degeneration (dots) in the vestibular nuclei in the cat following a lesion of the spinal cord at C_1. Principles of presentation as in Figure 5. Note abundant termination in group *x*, and restriction of termination within the lateral nucleus to its dorsocaudal regions. Abbreviations as in legend to Figure 1. From Pompeiano & Brodal (1957*b*).

berg (1960) are interspersed between the α neurons supplying the particular muscle. For physiological studies it is a further point of interest that during its course in the spinal cord the vestibulospinal tract changes its position, as seen from Figure 8.

The anatomical data reviewed above make it clear that the lateral vestibular nucleus of Deiters must be an important link in the pathways mediating cerebellar influences on the cord, in perfect agreement with physiological observations. In addition to the anterior and posterior vermis, also *the flocculonodular lobe may influence the nucleus of Deiters*, since fibres have been traced to it from the nodulus and the flocculus (Dow, 1936, 1938).

In view of the well developed cerebello-vestibulo-spinal paths via the *nucleus of Deiters, one might have expected that there would have been* correspondingly heavy projections in the opposite direction. This is not the case, however. In the first place we have not found any evidence (see Fig. 14) that the nucleus of Deiters sends fibres to the cerebellum (Brodal & Torvik, 1957). Secondly, the *spinal afferents to the nucleus of Deiters* are relatively scanty. In our study of this subject we (Pompeiano & Brodal, 1957*b*), furthermore, made an observation which appears rather puzzling. The spinovestibular fibres to the nucleus of Deiters (Fig. 9) turned out to end in its hindlimb region (cp. Fig. 6) only (where the fibres contact, at least chiefly, the large cells). Most of these fibres appear to come from low levels of the cord, which seems to "make sense".[1] When we (Walberg, Bowsher & Brodal, 1958) subsequently studied the *primary vestibular afferents to the nucleus of Deiters* it turned out that these do not supply its hindlimb region, but *are restricted to its forelimb (and neck) region*, i.e. its rostroventral part

[1] The distribution of spinal afferents within the nucleus of Deiters appears to be as in the cat, in the monkey (Mehler, Feferman & Nauta, 1960) and in man (Bowsher, 1962).

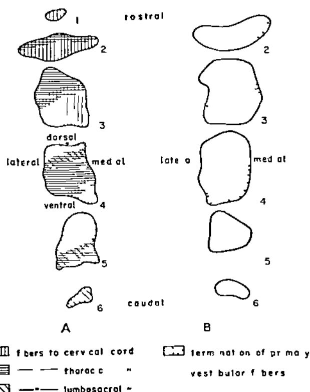


FIG 10 Diagram showing (*B*) the sites of termination of primary vestibular fibres (dots) in the lateral vestibular nucleus as seen in a series of transverse sections corresponding approximately to those seen to the left (*A*) showing the somatotopic pattern in the nucleus Note restriction of vestibular afferents to the forelimb region From Walberg Bowsher & Brodal (1958)

This is seen from Figure 5 and becomes more apparent when the sites of termination of primary vestibular fibres are entered in a diagram showing the somatotopic pattern in the nucleus (Fig 10) Figure 11 shows a photomicrograph illustrating this selective distribution (These afferents contact largely small cells)

These findings invite some comments The utricular macula appears to be the part of the vestibular apparatus which is particularly important for the tonic labyrinthine reflexes and as I have mentioned according to the studies of Lorente de Nó (1926 1933) the utricular macula appears to be the main source of vestibular afferents to the lateral vestibular nucleus

Since the vestibular impulses exert an influence not only on the tonic and reflex activities of the cervical cord but on the lumbosacral cord as well (see p 114 ff in Brodal Pompeiano & Walberg 1962 for a discussion) it appears intriguing that primary vestibular fibres reach only the forelimb (and neck) regions of the nucleus of Deiters This of course does *not* necessarily exclude an influence of vestibular impulses on cells in the dorsocaudal part acting on the lumbosacral cord Dendrites of cells in the latter part might extend into the forelimb part or into other regions of the

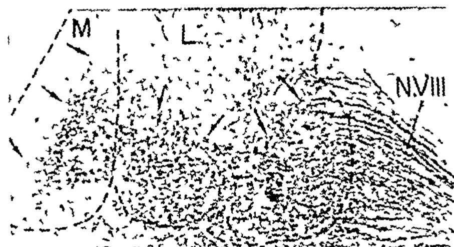


Fig. 11. A photomicrograph (×30) of a transverse section through the brain stem of a cat following complete destruction of the vestibular nerve (see Fig. 5. Nauta method), showing distribution of degeneration in vestibular nuclei. Borders of nuclei are indicated by broken lines. In the medial vestibular nucleus (M) degeneration at the level shown is restricted to the medial regions. *In the lateral nucleus (L) a relatively sharp border (arrows) is seen between the ventral* regions showing degeneration and the dorsal regions. Particularly in the latter some perikarya of Deiters' cells are visible. To the right, degenerating fibres entering in the vestibular nerve (N VIII). From Walberg, Bowsher & Brodal (1958).

vestibular complex in receipt of primary fibres. Cajal (1909–11) mentions *that dendrites of cells in the lateral nucleus (in the mouse) may extend beyond* its territory and enter the medial and descending nucleus. However, judging from a Golgi study of Hauglie-Hanssen in our laboratory (in preparation) this does not seem to be common, at least not in the cat. Practically all cells in the nucleus of Deiters have their dendrites within the confines of this, and furthermore, the cells in each of the two larger subdivisions (fore- and hindlimb regions) do not appear to extend their dendrites appreciably into the other. The question may, therefore, be raised whether vestibular impulses may reach the "hindlimb" region of the nucleus of Deiters via circumventral routes, for example via the cerebellum. In order to evaluate this possibility we will have to discuss the connections of the other vestibular nuclei.

The Relations of the Vestibular Nuclei to the Spinal Cord

In addition to the vestibulospinal tract, originating in the lateral vestibular nucleus and extending to the sacral cord, there are other *fibres to the cord from the vestibular nuclear complex, descending in the medial longitudinal fasciculus.* Concerning this projection rather divergent results have been published, largely, it appears, because the lesions of the nuclei in the experimental animals have not been sufficiently restricted. The suggestion of Carpenter (1960) and Carpenter, Alling & Bard (1960) that the descending nucleus *does not take part in the spinal projection* has recently been sub-

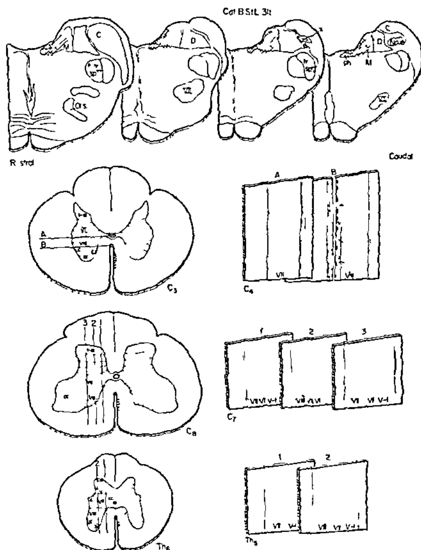


FIG 12 Diagrammatic representation of the findings in a case *with a lesion* restricted to the medial vestibular nucleus showing the course and sites of termination of *descending* fibres in the medial longitudinal fasciculus in the cat Abbreviations as in Figure 1 Cp Figure 8 From Nyberg Hansen (1964)

stantiated by Nyberg Hansen (1964) in our laboratory in experimental studies with silver impregnation methods Only the *medial nucleus* gives off fibres descending in the medial longitudinal fasciculus Figure 12 shows a diagram from one of Nyberg Hansen s cases with a lesion restricted to the medial vestibular nucleus As is seen the fibres do not descend beyond the upper thoracic segments and they are purely ipsilateral As to their sites of termination they resemble the vestibulospinal fibres since like these they establish synaptic contact with cells in Rexed s laminae VII and VIII only, and do not end on motoneurons

From a functional point of view it is interesting to compare the two fibre systems mediating vestibular influences on the cord. The rather massive somatotopically organized vestibulospinal tract descends to lowest levels of the cord and comes from the lateral vestibular nucleus, which is dominated by impulses from the utricular macula. In contrast, the medial vestibular nucleus, influenced, it appears, chiefly from the cristae, gives off a relatively modest spinal projection, not passing below the upper thoracic segments. However, both descending tracts end in laminae VII and VIII, and do not contact motoneurons (at least not in the cat). Little is known specifically of the physiology of the descending fibres in the medial longitudinal fasciculus. From the available anatomical data it seems permissible to conclude that by way of these fibres, coming from the medial vestibular nucleus, impulses from the cristae may exert an action on the muscles of the neck and forelimb.[1]

Just as the spinal afferents to the lateral vestibular nucleus are relatively scanty and restricted to a special part of it (its hindlimb region), so the *spinal afferents to the medial vestibular nucleus* are far from numerous (Fig. 9). From our study (Pompeiano & Brodal 1957*b*) it appears that they end only in the caudalmost part of the medial nucleus. Thus, spinal impulses can only to a limited extent be imagined to influence directly the action exerted by the vestibular nuclei on the spinal mechanisms.

On the whole, the spinal cord does not appear to have great possibilities for influencing the vestibular nuclei via direct connections. There are no spinal afferents to the *superior vestibular nucleus*, and apart from the relatively scanty spinal projections to the medial and lateral vestibular nuclei, there are only some fibres to the caudal part of the descending nucleus. The group x, however, which is probably to be considered a part of the descending nucleus, *receives a substantial spinal influx* (Fig. 9), *but it does not give off fibres to the cord.*

The Relations of the Vestibular Nuclei to the Cerebellum

As described in the previous section, connections from the vestibular nuclei to the cord are considerably more ample than those conducting in the opposite direction. As concerns the relations between the vestibular nuclei and the cerebellum, a somewhat similar principle is found. The cerebello-vestibular connections are far more abundant than the vestibulo-cerebellar.

As we have seen, the anterior and posterior vermis send fibres, arranged in a somatotopic order, to the dorsal half of the ipsilateral nucleus of Deiters (Fig. [illegible], to the left). In addition, its dorsal and ventral halves receive fibres, somatotopically arranged, from the rostral and caudal parts of the fastigial nucleus, respectively (see Fig. 7, to the right). It remains to consider the pro-

[1] Reference [illegible] was [illegible] above [illegible] restricted termination of primary vestibular fibres in the [illegible] part of the lateral vestibular nucleus (see Fig. 10). Thus, the muscles of the neck and [illegible] appear to be under a more direct control than the hindlimb muscles of vestibular [illegible] from [illegible] as well as from the cristae.

jection of these fibre systems onto other parts of the vestibular nuclei The *direct corticocerebello vestibular fibres* apart from those to the nucleus of Deiters are restricted to the dorsalmost part of the descending nucleus (Walberg & Jansen 1961) In contrast we found *fibres from the fastigial nucleus* to end in all four large vestibular nuclei (Walberg Pompeiano Brodal & Jansen 1962) as is seen from Figure 13 showing the total distribution of degeneration in the vestibular nuclear complex following a complete destruction of one fastigial nucleus Furthermore several of the small cell groups such as groups x and f (cp Fig 2B) receive fibres from the fastigial nucleus as does a slender column of cells which we have called the nucleus parasolitarius (N p s in Fig 13) From cases with lesions restricted to minor parts of the fastigial nucleus the details in this projection can be decided Concerning these the reader is referred to our original paper and our monograph (Brodal Pompeiano & Walberg 1962) Suffice it here to mention that just as in the nucleus of Deiters the fibres from the caudal and rostral parts of the fastigial nucleus supply in part different regions of the medial and descending nuclei Furthermore the fastigial fibres to the superior nucleus end largely in its peripheral parts (Fig 13) while its central part is the main terminal station of primary vestibular fibres (see Fig 5)

The cerebellovestibular fibre connections considered so far are all ultimately be they direct or synaptically interrupted in the fastigial nucleus derived from the anterior and posterior vermis that is from cerebellar regions often referred to as the spino cerebellum since they receive the bulk of afferent impulses from the cord However the *vestibular nuclei are influenced from the vestibular parts of the cerebellum the flocculo nodular lobe* as well According to Dow s (1936 1938) Marchi studies the nodulus sends fibres to all four large vestibular nuclei while the projection from the flocculus is restricted to the superior and lateral nucleus These connections have so far not been studied experimentally with silver impregnation methods and it is not unlikely that when this is done a more differentiated pattern may emerge within these projections However it is obvious that the spinal regions of the cerebellum must have far greater possibilities than the vestibulo cerebellum for influencing the vestibular nuclei

When we finally turn to the vestibulo cerebellar connections it will be seen that these do not reciprocate the cerebello vestibular ones Thus there are no direct routes for vestibular impulses to the spinocerebellum *Secondary vestibulo cerebellar fibres* i e fibres from the vestibular nuclei to the cerebellum have been traced in normal preparations and experimentally with the Marchi method (for a review see Jansen & Brodal 1958 p 236 ff) According to Dow (1936) they end in the flocculus nodulus uvula and fastigial nucleus chiefly ipsilaterally as shown in Figure 14 Studies of these connections with silver impregnation methods may reveal some details and clarify further data of interest for example their mode of ending Preliminary observations by Grant (1962) suggest that the fibres end as mossy fibres As to the exact origin of secondary vestibular fibres there has been some dispute

Fig. 13 Diagrammatic representation of the distribution of degeneration in the vestibular nuclei following total destruction of one fastigial nucleus (hatchings above). The distribution is bilateral since fibres from the caudal part of the fastigial nucleus cross the midline. Note that the distribution of degeneration is not equal on the two sides. Symbols as in Figure 5, abbreviations as in Figure 1. From Walberg, Pompeiano & Brodal (1962).



Fig. 14. A summarizing diagram of the secondary vestibulocerebellar projection in the cat. The fibres come from the regions dotted in the diagram of a horizontal section through the vestibular nuclei, namely the ventrolateral part of the descending nucleus (including groups *f*, not indicated), the caudal part of the medial vestibular nucleus, and group *x*. The course of the fibres and their sites of termination are indicated according to Dow (1936). From Brodal & Torvik (1957).

In a study with the method of retrograde degeneration (modified Gudden method, Brodal 1940) we (Brodal & Torvik 1957) found them to be derived from certain parts of the medial and descending nucleus only, as seen from the dots in Figure 14. In addition the group x as well as the group f in the descending nucleus (the latter not indicated in Fig. 14, see Fig. 1) send fibres to the cerebellum. It is of some interest to notice that those regions of the vestibular complex which project onto the cerebellum do not receive primary vestibular fibres or only a modest number. Particularly striking are the rather marked cerebellar projections of the groups f and x (Brodal & Torvik 1957) which do not receive primary vestibular fibres (Walberg, Bowsher & Brodal 1958). One may therefore have some doubts whether the secondary vestibulocerebellar fibres are at all concerned with the transmission of vestibular impulses to the cerebellum (its flocculo-nodular lobe).

That this, however, receives vestibular impulses by way of *primary vestibulocerebellar fibres*, having their perikarya in the vestibular ganglion, is learnt from several experimental studies, all of them except one (Carpenter 1960) performed with the Marchi method. These fibres are described as ending in the flocculus, nodulus, ventral part of the uvula and in the fastigial nucleus, a few probably in the lingula. Concerning their mode of termination in the cerebellar cortex, i.e. whether they end as mossy or climbing fibres, diverging opinions have been held. The last problem can be solved only in experimental studies with silver impregnation methods following transection of the vestibular nerve. Using this approach we have found the primary

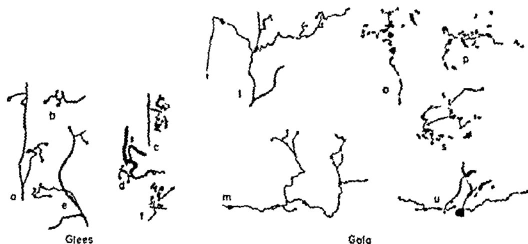


Fig. 17. Free-hand drawings of normal mossy fibre terminals as they appear in Glees (left) and Golgi sections (right). To the left in both groups mossy terminals from the anterior lobe (*a*, *b*, *e*, *i*, *m*), to the right from the flocculonodular lobe (*c*, *d*, *f*, *o*, *p*, *s*, *u*). From Brodal & Drabløs (1963).

that the collaboration between the vestibular apparatus, the cerebellum and the spinal cord is a very complicated affair, which will not be easy to clarify.

Concluding Remarks

The data presented in this review as well as other results of studies of the fibre connections of the vestibular nuclei show us a very complex pattern of interrelations between the individual vestibular nuclei and cell groups and between these and the peripheral vestibular apparatus, the spinal cord and the cerebellum. The vestibular nuclear complex may be considered as a mosaic of minor units, each of them having its particular pattern, especially with regard to its fibre connections. There is still much to be done before the anatomical organization of the vestibular nuclei is known in as great detail as is desirable. The clarification of the minute anatomy of the vestibular nuclei may give hints concerning functional aspects, but these can only be established in meticulous neurophysiological investigations. We believe that the recent studies of the anatomy of the vestibular system will be of use in such studies in the future and we may hope that they will serve as a stimulus to continued research, physiologically as well as clinically, of the vestibular system.

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EXPERIMENTAL CEREBELLAR LESIONS AND THEIR EFFECT ON VESTIBULAR FUNCTION

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The cerebellum has been studied extensively following damage evoked by surgery, disease or other causes, in order to determine its afferent and efferent connections and also its functional organization including the vestibulo-cerebellar relationships. Extensive references regarding these matters can be found in the works of Dow & Moruzzi (1958), Jansen & Brodal (1954), Brodal, Pompeiano & Walberg (1962) and others.

In this paper we discuss our experiences which have been accumulated over the last five years on disorders of vestibular function associated with cerebellar lesions in the cat. This experience is based on a large series of animals with a variety of lesions involving the corpus cerebelli or the flocculonodular lobe or both (Table 1). The discussion is restricted to disorders of vestibular function associated with cerebellar damage. Other signs which may be associated with cerebellar lesions are not considered.

We wish to emphasize that the functional organization of both the cerebellar and vestibular systems of the cat differ widely from those of man. Parallelism between the two species can be made only on a comparative basis.

The lesions were produced by surgically exposing the desired cerebellar area and then ablating one or more folia by means of suction. The location and extension of the cerebellar damage was defined histologically in each animal but no attempt was made to determine degeneration of neural pathways associated with the lesions.

Since our experience regarding the effect of ablating various lobules of the posterior lobe is limited, the discussion will be restricted to our experiences with the flocculonodular and anterior lobes.

The Flocculonodular Lobe

It is well established that the afferent and efferent connections of the flocculonodular lobe are mainly with the vestibular system. Anatomical data has revealed important differences in innervation between flocculus and nodulus. The efferent connections of the former are mainly with Deiters

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TABLE 1 *Number of animals with cerebellar damage*

Flocculus	7	Paraflocculus	2
Nodulus	51	Tuber vermis	2
Anterior lobe	16	Pyramis	2
Ans form	3	Uvula	2
Paramedian	2		

and Bechterew nuclei while the efferents of the nodulus terminate in all vestibular nuclei nucleus fastigii dorsal reticular formation and the medial longitudinal fasciculus The difference in innervation may account for differences in functional properties between the two structures as revealed by comparative observations (Dow 1938 Carrea 1946 Carrea & Metler 1947, Manni 1950)

Ablation of the Flocculus

Histological cerebellar studies of seven cats with unilateral ablation of the flocculus showed in all instances that small or large damage to the overlying paraflocculus was produced The functional changes associated with the ablation divided the series into two groups One group of three cases presented a mild transitory unsteadiness of gait no spontaneous or positional nystagmus and rotatory reactions within normal limits The lesion in one case is illustrated in Figure 1 (Cat A 346) The other group of four animals exhibited similar histopathological damage (Fig 1 Cat A 506) but these cats presented several signs of vestibular disturbance such as disequilibrium and positional nystagmus The disorder of equilibrium consisted of an unsteady gait and swaying of the body or lateral pulsion toward the side of the lesion The disturbance was mild and lasted for about two weeks The positional nystagmus was mainly direction changing in type which often presented as bouts of paroxysmal nystagmus After the third postoperative week the cats exhibited no signs of vestibular disorder

The almost negative results of the first group raised the question as to whether the vestibular disturbances of the second were due to the ablation or to other factors It is possible that the signs may have been caused by circulatory changes edema and/or surgical trauma of structures located in the cerebellopontine angle

Ablation of the Nodulus

In our experience and that of others surgical ablation of the nodulus was always accompanied by damage to the uvula The damage to the latter varied from a small superficial degenerative process of one folium to total destruction as shown in Figure 2

So far the data on ablations of the nodulus (Dow 1938 Spiegel & Scala 1942 Carrea 1946 Carrea & Metler 1947 Manni 1950 Dow & Moruzzi

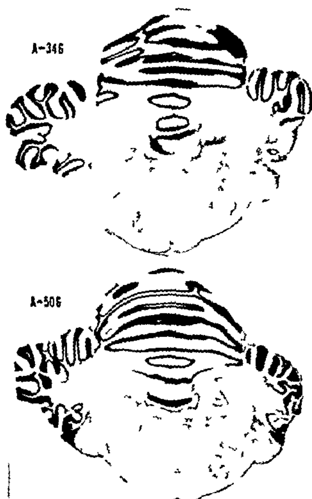


FIG 1 Ablation of right flocculus in Cat A 346 and A 506 In both cases the lesion encroached upon the overlying paraflocculus *Nissl s stain*

1958 Fernandez 1960) had resulted in a syndrome consisting of (1) disequilibrium without cerebellar ataxia (2) positional nystagmus of several types including the so called benign paroxysmal and (3) prolonged vestibular reactions to rotatory and caloric tests (Fig 3)

It is believed that these vestibular disturbances represent a release of vestibular centers from cerebellar inhibition This hypothesis assumes that *the nodulus acts as an inhibitor of sensory vestibular input* Implicit in this assumption is the notion that the sensory input at the peripheral level is not modified by the nodulectomy The vestibular disorders seem to reflect a disarray of the integrating mechanism of sensory signals in the central nervous system

The following argument is a rational consequence of the hypothesis If the vestibular disorders associated with ablation of the nodulus represent a release of vestibular centers from cerebellar inhibition then stimulation of



Fig. 9. Ablation of nodulus and uvula of cat A 1015. Weil's stain.

the nodulus may lead to depression of vestibular responses. The argument was supported by means of electrical stimulation of the nodulus described below.

Electrical Stimulation of the Nodulus

In a series of 12 cats either one pair of stainless steel wires were implanted stereotaxically in the midline of the nodulus or two pairs of electrodes were implanted, one in the right and the other in the left side. The steel electrodes (0.3 mm in diameter) were totally isolated with enamel save for their tips. The pair was formed by twisting two wires so that the diameter of the pair at the tip was approximately 1.0 mm. The pair or pairs of electrodes were placed stereotaxically according to the coordinates calculated by Snider & Niemer (1962) and then fixed to the skull with dental cement. Several days following recovery the cat was secured in the animal box as described by Henriksson, Fernández & Kohut (1960). Some animals broke their electrodes probably by rubbing their heads against their cages. In these cases the tail of the electrode was exposed by reopening the wound under local anesthesia. When necessary the dental cement was drilled down to obtain sufficient electrode length for purposes of stimulation.

The nodulus was stimulated electrically with 300 monophasic or biphasic pulses per second. The duration of each pulse was 0.5 msec and the duration of each train of pulses was varied from a few seconds to one minute. The

Ablation of nodulus and uvula

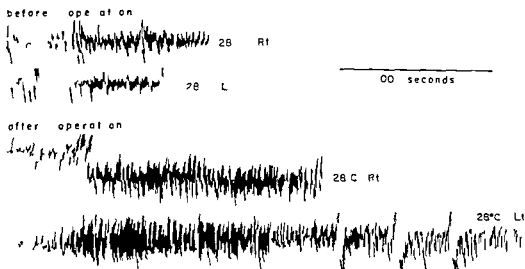


FIG 3 Caloric tests of cat A 1015 performed before and after ablation of the nodulus and uvula The postoperative records were obtained one week after the ablation Note the considerable increase in postoperative caloric reactions

intensity of stimulus was also varied but kept below the threshold of facial muscle contraction The eye movements elicited by stimulation of the nodulus were observed directly or recorded electronystagmographically No other reflexes were observed due to limitations imposed by the experimental conditions Upon completion of the experiment the animals were sacrificed by intravital perfusion of buffered 10 % formalin solution The cerebellum and medulla were removed and processed to determine path and placement of the electrode tips

The data shows that in the conscious cat no eye movements were observed during bipolar stimulation through any pair of electrodes or between two pairs We did not consider any eye movements accompanied by contraction of facial muscles In these cases any effect is probably due to the spread of current to other cerebellar and/or medullary structures

Electrical stimulation of the nodulus during nystagmus elicited by both rotatory or caloric tests produced a consistent inhibitory effect The nystagmus stopped within a second of initiation of the electrical stimulus and reappeared as soon as the stimulus was discontinued The effectiveness of the current was a function of several parameters such as duration frequency and voltage of the pulses It also varied from one animal to another and with the placement of the electrodes

A representative case illustrating the placement of electrodes in the right and left sides of the nodulus is shown in Figure 4 The electrodes were placed laterally in the rostral surface of the nodulus The inhibitory action of small voltages applied between the two pairs is presented in Figure 5 A similar



Fig. 4. Placement of two pairs of electrodes in cat A 1391. The arrows point to the location of the electrode tips in the right side (*A*) and left side (*B*) of the nodulus. The paths through the cerebellar tissue are not seen in these sections. Klüver's stain.

result was obtained when the right or left pair was stimulated alone (Figs. 6 and 7).

An interesting finding associated with the inhibition of nystagmus was that the eyes presented a conjugate deviation toward the side of the slow component. Figure 8 illustrates a case showing the placement of the left pair of electrodes and Figure 9 the effect of stimulation. It is observed that inhibition of nystagmus to the right (water at 20°C in the left) was followed by a conjugate movement of the eyes to the left (upward displacement of the baseline). Inhibition of the left beating nystagmus was accompanied by right conjugate deviation (downward displacement of the baseline). The conjugate deviation was confirmed by both electronystagmography and direct observations of the eyes. This effect of stimulation suggests strongly that the inhibitory action is upon the neural mechanism underlying the rhythm of nystagmus. The mechanism is probably located in the vestibular centers formed by vestibular

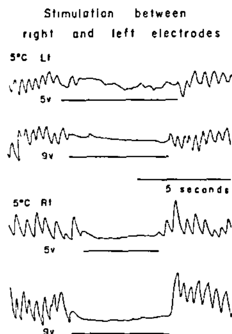


Fig 5

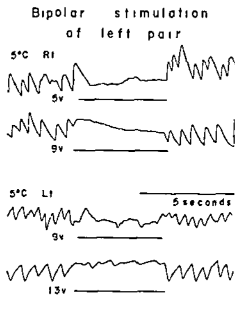


Fig 6

Fig 5 Inhibition of caloric induced nystagmus as a result of electrical stimulation between right and left pairs of electrodes in cat A 1391 Observe the rapid effect of the inhibitory action and the immediate resumption of nystagmus after cessation of the stimulus

Fig 6 Inhibition of nystagmus during stimulation of the left pair of electrodes in cat A 1391

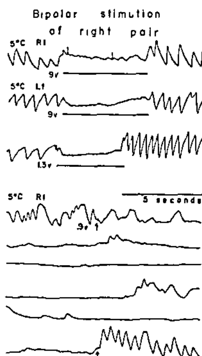


Fig 7 Inhibition of nystagmus during stimulation of the right pair of electrodes in cat A 1391 During the nystagmus elicited by irrigation of the right ear with water at 5°C, the stimulus was applied for a full minute Observe that inhibition was maintained throughout this period



Fig 8 Path of one pair of electrodes through the cerebellum of cat A 1380 The tips were just within the left side of the nodulus

nuclei and the reticular formation More specifically stimulation seems to inhibit the mechanism from whence the fast component of the nystagmus originates, while the mechanism of the slow component is not affected

Recapitulating these experiments support strongly the opinion that in the cat the nodulus has an inhibitory action upon the vestibular responses, at

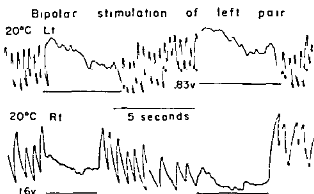


Fig 9 Conjugate deviation of the eyes in cat A 1380 Calorization with water at 20 C in the left ear elicited nystagmus to the right Electrical stimulation inhibited it and produced conjugate deviation of the eyes to the left as shown by the upward displacement of the baseline Calorization of right ear with water at 20 C elicited nystagmus to the left Conjugate deviation of the eyes to the right (downward displacement of the baseline) occurred during electrical inhibition of the nystagmus

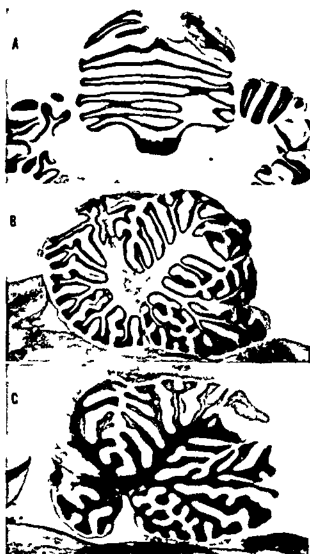


Fig. 10. Photomicrograph of small (A), medium (B) and large (C) damage of the vermis proper of the anterior lobe. A and B, Nissl's stain; C, Weil's stain.

least on the vestibulo-ocular reflex arc. It appears that the inhibitory impulses are acting on the neural mechanism of the fast component of nystagmus. We would like to emphasize that we have no strong evidence to rule out the possibility that this effect may be due to spread of current to other structures.

Ablation of the Anterior Lobe

The anterior lobe has been studied more extensively than any other cerebellar segment. The anatomical studies of its afferent and efferent con

nections in mammals define three longitudinal areas the vermis proper the intermediate part and the lateral part In the cat the lateral part is absent (Jansen & Brodal 1954) The division is supported by physiological studies demonstrating a longitudinal somatotopic localization

The main efferent connections of the vermis proper are with the rostral half of the nucleus fastigii and with the vestibular nuclei The fibers of the former seem to terminate in the reticular formation of the medulla and pons and in the superior lateral and descending vestibular nuclei These connections raised the question as to whether localized or extensive lesions of the vermis proper and/or fastigial nucleus may be associated with alterations in vestibular function We have no experience with the effects of lesions involving the nucleus fastigii and/or other cerebellar nuclei upon vestibular function The data from the literature (see Brodal Pompeiano & Walberg 1962) indicates that spontaneous or positional nystagmus is not associated with lesions localized to the cerebellar nuclei Figure 10 is taken from a series of animals with small or large lesions in the vermis proper of culmen and centralis These animals did not exhibit asymmetric posture of the head or body Strong rigidity of the forelegs and an unsteady gait were the most prominent features There was no spontaneous or positional nystagmus although both were transiently seen during recovery from the barbiturate anesthesia The vestibular responses to rotatory and caloric stimulation may be somewhat depressed for a week or more

Recapitulating our series indicates that small or large ablations of the vermis proper of the anterior lobe did not produce definite signs of a vestibular disorder

SUMMARY

Disorders of vestibular function were studied in a series of cats with damage to either flocculus nodulus or anterior lobe of the cerebellum Unilateral ablation of the flocculus yielded contradictory results Some animals presented disequilibrium and positional nystagmus while others exhibited little or no vestibular disturbance It is suggested that the signs of the former group may have been due to vascular disturbances edema or surgical trauma involving the cerebello pontine angle

Ablation of the nodulus was associated with disequilibrium positional nystagmus and prolonged vestibular reactions to rotatory and caloric tests The findings support the hypothesis that the nodulus acts as an inhibitor of sensory signals to the vestibular centers formed by the vestibular nuclei and the reticular formation This hypothesis was supported by producing inhibition of vestibular responses as a result of electrical stimulation of the nodulus Ablation of the vermis proper of the anterior lobe produced few if any signs of vestibular disorder

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NYSTAGMUS FOLLOWING STIMULATION IN THE CENTRAL VESTIBULAR PATHWAYS USING PERMANENTLY IMPLANTED ELECTRODES

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INTRODUCTION

In clinical neuro-otological examinations the observation of nystagmus is an essential part. The aim of such examinations is to reach a diagnosis, if possible pointing to a topographical localization. It is, however, rather difficult to collect clinical material where the nystagmus findings can be correlated with structural changes within the central nervous system. Where this is possible there are usually generalized changes due to increased intracranial pressure, dislocations by tumors, vascular processes etc., which complicate the analysis of the material. It is thus difficult to establish with certainty that a lesion localized to any specific central region may have elicited the nystagmus. It is therefore desirable to turn to animal experiments in parallel with clinical nystagmography.

The aim of this investigation was to study the central vestibular pathways with special regard to spontaneous and positional nystagmus. It has been shown in a large series of experiments (Aschan *et al.* 1956*a*, *b*, 1958 and Aschan 1958) that alcohol intoxication in man produces a typical positional alcohol nystagmus (PAN). This PAN shows a clear correlation with the blood alcohol concentration. The peripheral labyrinthine function plays an important part in the elicitation of this PAN both in animal (de Kleyn and Versteegh 1930) and in man (Aschan *et al.* 1964), central nervous processes must also be involved, however. In animals the first phase of PAN can be provoked by alcohol intoxication with the same regularity as in man. It should be possible to study the central nervous mechanism of PAN further by animal experiments.

EXPERIMENTAL APPROACH

Electrode pairs were permanently implanted in the central vestibular pathways in 63 rabbits. When the animals had recovered from the operations

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stimulation was applied over the differently situated electrodes and the nystagmus provoked recorded by nystagmography. The influence of stimulation on the PAN was also studied. Electrocoagulation was later performed around the electrode point and during a certain period experiments similar to those performed previously during stimulation were repeated. The purpose was to study the effects of stimulation and of destruction of the same region. After intravital perfusion fixation the brain was removed. Following further fixation blocks were taken for serial sectioning and staining. The location of the points of the electrode canals and the regions which had been electrocoagulated were established.

METHODS

Rabbits were chosen as experimental animals because they are easy to handle and because nystagmus can easily be recorded from them without anaesthesia. We followed the neuro-anatomical description of the rabbit's brain stem given by Meessen & Olszewski (1949) and Brodal's (1940) topographical atlas of the folia of the rabbit's cerebellum. Stereotactic references were taken from the atlas of Monnier & Gangloff (1961) but had to be adjusted since this atlas is not planned for the brain stem or the cerebellum.

The electrodes were made from 0.3 mm platinum-iridium sharpened to a fine point at one end. The electrical isolation and at the same time the necessary stiffness was provided by lacquering with a very thin varnish, the electrodes being heated between each dipping. This procedure was performed in such a way that only the point of the electrode was left unisolated, its area having a diameter of about 10 microns. All electrodes were checked in an electrolyte bath before use.

Two parallel electrodes 0.5–1 mm apart and slightly different in length were implanted to make it easier to hit the region intended and in order to study the spreading of the electrical stimuli. The positions of the electrodes were checked by X-ray, which also provided information about the sinuses and the middle ears of each animal. Infections could thus be diagnosed in some animals in this way and those animals were removed from further experiments.

Electrocoagulation was usually produced by passing 1.0 mA through the electrode for 30 seconds. In Fig. 1 two examples demonstrate that by using different times for the electrocoagulation it is possible to control the size of the region coagulated. The two figures represent the same magnification and the lesion in rabbit 92 with electrocoagulation to the right from the midline in lobulus α in the cerebellum represents the standard type of lesion used in this investigation.

The implanted electrode was made negative and the positive electrode was applied deep in the neck. The electrocoagulation also served as a control of electrical leakage. Alternative electrical pathways result in electrocoagula-

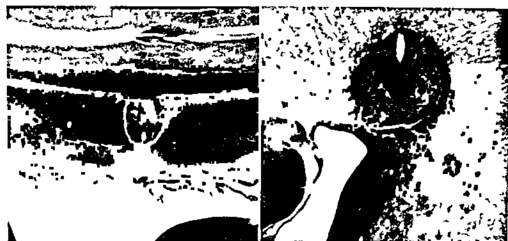


Fig 1 Electrocoagulation with 1 0 mA for 30 seconds (rabbit 92) to the left and 60 seconds (rabbit 93) to the right The magnification is the same in both slides Note the possibility of regulating the size of the area coagulated The electrocoagulation in rabbit 93 localized on the right side in the nodulus shows the standard size used in this investigation 11 days between coagulation and perfusion

tions elsewhere than at the electrode point and are discovered at the subsequent neuro anatomical examination

All the electrodes were implanted through the anterior parts of the cerebellar lobulus c, the reason being that this part is known to have very few (if any) direct connections with the vestibular nuclei (Walberg & Jansen, 1961) and is known not to receive any vestibular fibers (see Jansen & Brodal, 1958)

The stimulations were performed with a Disa Multistim instrument, type 13G04 Rectangular pulses were used After preliminary experiments 200 pulses per second and a pulse length of 0 3 ms proved to be the best for provoking nystagmus both in the brain stem and in the cerebellum A frequency of 50 pulses per second or lower proved to be more suited for inducing motor reactions from the Vth and VIIth cranial nerves Such reactions were always tested After a comparison with the neuro anatomical data such reactions combined with the nystagmus gave an idea of the spreading of the stimuli With a standard resistance over the electrodes of about 50 kΩ 2 volts constant voltage stimulation elicited responses within an estimated radius of 200–400 microns around the point of the electrode The facial motor function in particular gave considerable information due to the complex topography of the VIIth nerve in the brain stem Tests with only a few pulses but a comparatively high voltage also provided information about the spread of the stimulus and its relation to the voltage

Nystagmography was carried out with the same methods as described for man by Aschan (1955) and Aschan *et al* (1956*a*) The electrodes around the eye however, consisted of surgical clips which were applied to the skin

The animals were killed under nembutal anaesthesia and submitted to

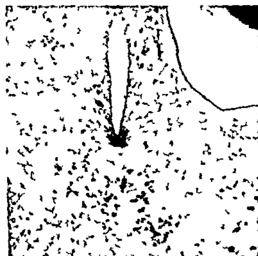


Fig 2



Fig 3

Fig 2 The histological picture 61 days after implantation of an electrode point ventro rostral to the superior vestibular nucleus (rabbit 79) No electrocoagulation and the electrode was still active at the time before the perfusion Note the rather small reaction at the point after this long period

Fig 3 Sagittal section through the cerebellum demonstrating a very modest cellular reaction along an electrode canal three weeks after electrode implantation (rabbit 101)

perfusion fixation according to the method described by Koenig Groat & Windle (1945) The electrodes were removed from the skull and the central nervous system rostrally to the third cervical cord segment was removed and placed in 10 % neutral formol saline for at least 3 days Photographs were taken of the part of the cerebellum through which the electrodes had been inserted The cerebellum was usually separated from the rest of the brain embedded in paraffin and cut in serial sagittal sections at 20 microns Every second section was stained with thionine Remaining sections were saved *The brain stem was cut in the same way with the exception that* transverse sections were used Some cerebella which were not separated from their brain stems were cut in transverse sections The purpose of examining the sections from the central nervous system was not only to find out the location of the electrode point We could see e g that the electrode point gave a rather small reaction in some preparations where the electrode had been left for a long time and no electrocoagulation performed The electrode in Fig 2 was left implanted for 61 days still active and the glia reaction around the point was rather modest In addition the neuro anatomical examination served as a control of extraneous lesions i e infections etc One animal for example showed no spontaneous or positional nystagmus and inspection macroscopically after fixation gave no indication of a big cerebellar abscess which was found at the neuro anatomical examination 15 % of the material had to be excluded due to such findings Usually how

ever the clinical picture especially the nystagmus behaviour following the electrode implantation showed that something was wrong and the animal could be excluded at an early stage

RESULTS

Nystagmography in Rabbits

In clinical nystagmography Aschan (1955) and Aschan *et al* (1956) pointed out that visual influences as a rule inhibited vestibular nystagmus often making it impossible to observe or record a nystagmus unless all visual influences were abolished This means that the nystagmus should be recorded in complete darkness or behind closed eyelids

When observing and recording nystagmus after central lesions it was very often found at the start of these investigations that a nystagmus disappeared within 24 to 48 hours One possible explanation was that it was caused by oedema and similar changes and when these pathological conditions regressed or disappeared the nystagmus disappeared also This was contradicted however by another observation that albino rabbits always demonstrated a much longer period of nystagmus than pigmented rabbits with apparently the same lesion This latter observation made it necessary to record nystagmus systematically in the animal under different visual conditions

The records in Fig 4 demonstrate an acute experimental condition with positional alcohol nystagmus (PAN) in a rabbit The nystagmus induced by a single dose of alcohol was recorded and observed first in light and immediately afterwards in darkness In the first two pairs of records slight differences in intensity were observed the highest being recorded in darkness Later when the blood alcohol concentration decreased this difference became more and more marked If for example the minimum blood alcohol concentration necessary for producing PAN is studied direct observations give a value of 2 4 per mille whereas records in darkness give a threshold of about 1 4 per mille

In the experiments with central lesions in the rabbit the systematic follow up study of the nystagmus represents a prolonged or chronic experimental situation Fig 5 demonstrates findings from rabbits with a central lesion The upper pair of records show that in light no nystagmus is present and furthermore visual inspection in light revealed no nystagmus The day after the operation this particular animal showed nystagmus both in light and in darkness but one week later nystagmus was detected only in darkness

The follow up which is illustrated here only with the records taken one week after the operation proved that the disappearance of the nystagmus was due to visual influences—fixation

A further example is given in Fig 6 In this case there was a bilateral cerebellar lesion In light only a left beating horizontal nystagmus was seen and recorded in the left lateral position of the head and body Under the last

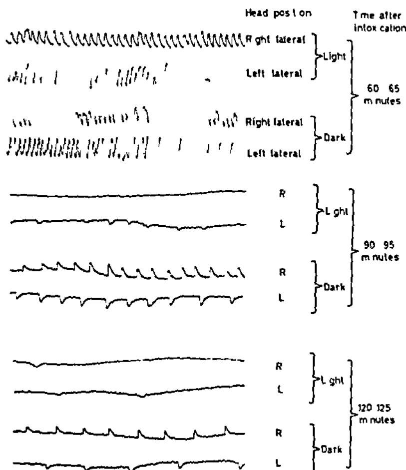


FIG 4 Normal rabbit given 11 cc 45 per cent alcohol intravenously Weight 3 1 kg Positional alcohol nystagmus (PAN) recorded at different intervals after the injection At each observation two pairs of records were made with open eyes in light and in complete darkness The lower intensity of the nystagmus in light as compared with that in darkness is easy to observe in any of the pairs of records

mentioned experimental conditions no nystagmus was observed in the right lateral position In darkness however a positional nystagmus was recorded in both lateral positions right beating in the right lateral and left beating in the left lateral position of the body There were differences in the intensity between the right and left beating nystagmus as well as between the left beating nystagmus in light as compared with that in darkness

In Fig 6 it is of interest to note that this cerebellar lesion produced a positional nystagmus with all the qualities of a PAN even though no alcohol was used in this animal

The findings concerning the visual influences on vestibular nystagmus in the rabbit were made systematically in all the experiments These observa

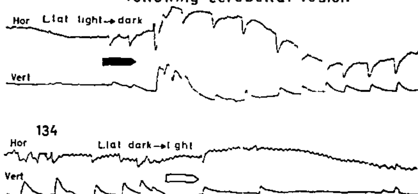


Fig 5 Rabbits 133 and 134 with cerebellar lesions One week after the operation no nystagmus could be observed or recorded in light but in complete darkness the same nystagmus as observed the day after the operation could be recorded (upper records) In rabbit 134 (below) the nystagmus recorded in complete darkness quickly disappears when light is introduced

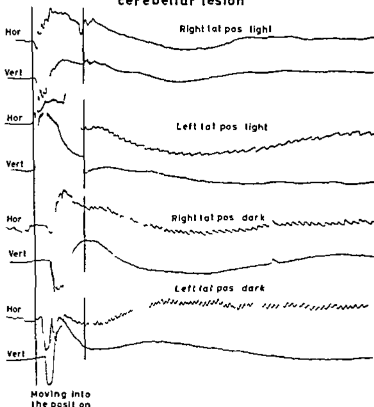


Fig 6 Bilateral cerebellar lesion (rabbit 137) No alcohol intoxication Records made 2 weeks after operation In light only a left beating horizontal nystagmus in the left lateral position is observed and recorded In complete darkness a right beating horizontal nystagmus is recorded in the right lateral position in addition In darkness the left beating nystagmus in the left lateral position shows a marked increase in intensity when compared with that recorded in light

tions show that nystagmography is the only way, and necessary for all types of vestibular experiments, for evaluating nystagmus Furthermore, our findings provide one explanation for some rather contradictory results concerning nystagmus observations following lesions in the vestibular system, reported in the literature

Nystagmus Following Stimulation

Stimulations with the electrode point located in the vestibular nuclei often resulted in nystagmus When a nystagmus response was observed and recorded this nystagmus always had the same intensity, as long as the stimulus was going on The stimulations were always performed with the animal in different positions the whole animal being turned in a posture box Fig 7 demonstrates the nystagmus records from an animal with the electrode point in the centre of the right triangular or medial nucleus in rostro caudal direction somewhat caudal to its middle The records are the same in all respects in the three positions two lateral and one erect, and the nystagmus can be regarded as a spontaneous nystagmus The stimuli were identical in the three records

In the cerebellum the stimulations were concentrated to lobulus *a* the nodulus When the electrode point was located in the lateral parts of the nodulus a nystagmus was provoked by stimulation over the electrode This nystagmus, however, contrary to nystagmus induced by stimulation in the vestibular nuclei was always influenced by the position of the body Electrode points localized in or close to the midline of the nodulus did not seem to induce any nystagmus

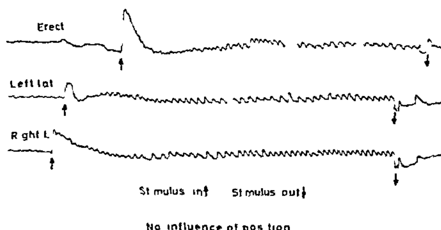


Fig 7 An electrode point in the right triangular (medial vestibular) nucleus somewhat caudal to its middle (rabbit 129) Identical stimulations in three different positions result in right beating nystagmus with the same intensity in the three positions i e right beating spontaneous nystagmus

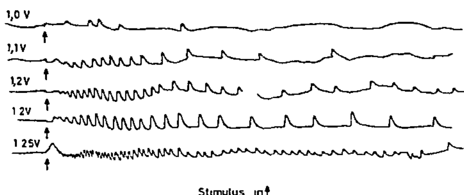


FIG 8 An electrode point apical and to the right in the cerebellar nodulus (rabbit 106) All records made in erect position Varying voltages Note increase in the intensity of nystagmus with increasing voltage No habituation on repetition of the same stimulus—1 2 volts All records show for the first 5-7 seconds a high nystagmus intensity which then decreases levelling out to constant values Compare with Fig 7 (brain stem stimulation)

The records obtained by stimulation over an electrode which was located in the nodulus on the right side (cf Fig 1) are demonstrated in Figs 8–9 *In Fig 8 all the records refer to the animal in the erect position* Increasing voltage results in increasing intensity of nystagmus During the first seconds after the beginning of the stimulation the intensity of the nystagmus increases and then gradually decreases to come to a constant intensity In

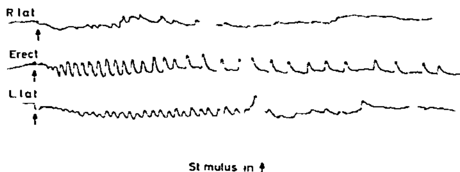


FIG 9 Records from the same rabbit as in Fig 8 Three different positions Note the different results from the same stimulus Compare with Fig 7 (brain stem stimulation)

tions show that nystagmography is the only way, and necessary for all types of vestibular experiments, for evaluating nystagmus. Furthermore, our findings provide one explanation for some rather contradictory results concerning nystagmus observations following lesions in the vestibular system, reported in the literature.

Nystagmus Following Stimulation

Stimulations with the electrode point located in the vestibular nuclei often resulted in nystagmus. When a nystagmus response was observed and recorded this nystagmus always had the same intensity as long as the stimulus was going on. The stimulations were always performed with the animal in different positions, the whole animal being turned in a posture box. Fig. 7 demonstrates the nystagmus records from an animal with the electrode point in the centre of the right triangular or medial nucleus, in rostro caudal direction somewhat caudal to its middle. The records are the same in all respects in the three positions, two lateral and one erect, and the nystagmus can be regarded as a spontaneous nystagmus. The stimuli were identical in the three records.

In the cerebellum the stimulations were concentrated to lobulus *a*, the nodulus. When the electrode point was located in the lateral parts of the nodulus a nystagmus was provoked by stimulation over the electrode. This nystagmus, however, contrary to nystagmus induced by stimulation in the vestibular nuclei was always influenced by the position of the body. Electrode points localized in or close to the midline of the nodulus did not seem to induce any nystagmus.

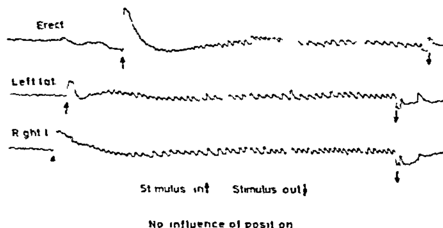


FIG. 7. An electrode point in the right triangular (= medial vestibular) nucleus somewhat caudal to its middle (rabbit 129). Identical stimulations in three different positions result in right beating nystagmus with the same intensity in the three positions, i.e. right beating spontaneous nystagmus.

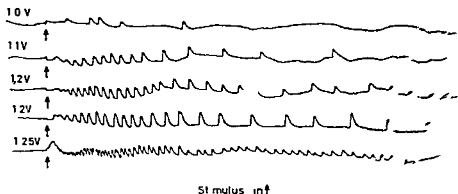


Fig 8 An electrode point ap cal and to the right in the cerebellar n [illegible]
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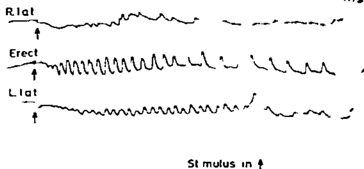


Fig 9 Records from the same rabbit as in Fig 8 Three [illegible] results from the same stimulus Compare with Fig 7 (brain st m[illegible]

Fig 9 the three records refer to different positions of the body. The same stimulus was used in all the positions. The differences in the intensity of the nystagmus between the three positions are very marked. Repeated tests showed that it was actually the position of the body and not repeated stimulation producing habituation or similar phenomena that was responsible for the changes in the intensity of the nystagmus.

The Effect of Stimulation on Positional Alcohol Nystagmus (PAN)

In all the animals positional alcohol nystagmus was induced by injecting intravenously 45 % alcohol in Ringer's solution, the dose being adjusted to the body weight. 3.5 cc per kilo always produced a PAN lasting for 60 minutes or more. A typical control experiment has been demonstrated in Fig 4.

In the erect position the intoxicated animals do not show any nystagmus. The alcohol intoxication produced a marked change in the results obtained by stimulation prior to the intoxication. Thus stimulation with voltages that prior to the intoxication resulted in nystagmus were completely or nearly completely ineffective in the intoxicated animal. This finding was the same both in animals with electrodes in the nodulus and with such in the vestibular nuclei. When the animals had recovered from the intoxication, however, they responded to electrode stimulation as before.

In the lateral positions the intoxicated rabbit showed the usual PAN demonstrated in Fig 4, beating to the right in the right lateral and to the left in the left lateral positions of the body. In these lateral positions, however, stimulation with voltages that had produced nystagmus prior to the intoxication had a marked effect on PAN. Stimulations in the vestibular nuclei, however, gave different responses as compared with stimulations in the cerebellum.

Nystagmus following stimulation in the brain stem was described above as spontaneous, independent of the position. The effect of the stimulation on PAN was easy to characterize. Stimulation over an electrode in the vestibular nuclei that for example produced right beating nystagmus in the unintoxicated animal (Fig 7) increased the right beating and decreased the left beating PAN in the intoxicated animal. If the stimulus voltage was increased it even caused a change in the beating direction (Fig 10). As long as the stimulation was going on the effect was unchanged. Electrodes with their points in the brain stem which did not give nystagmus in the unintoxicated rabbit had no effect on PAN.

Stimulation over electrodes in the nodulus produced another type of response. The intensity of PAN was always affected, even in those animals with electrodes in or close to the midline in which stimulation prior to the intoxication apparently failed to induce nystagmus. Lateral electrodes as a rule had an inhibitory effect on PAN in the ipsilateral position, while those near to or at the centre had an inhibitory effect in both lateral positions.

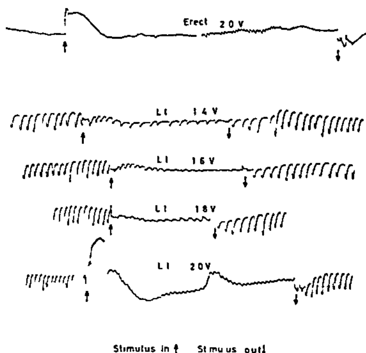


Fig 10 An electrode point in the right triangular nucleus (rabbit 129) Stimulation on the unintoxicated animal shown in Fig 7 Stimulation in erect position during alcohol intoxication gives quite another answer but the right beating nystagmus is visible at the end of the first record The other records demonstrate the effect on PAN of stimulation with increasing voltage (left lateral position) 1 4 volts decrease the intensity of PAN 1 6 volts make it partly disappear At 1 8 volts change in beating direction still more marked at 2 0 volts

Fig 11 will serve to illustrate this effect The electrode point was located in the right side of the nodulus In the right lateral position the inhibition of PAN is easy to see The voltage of 2 0 volt decreases the intensity continuously and the slight increase in voltage to 2 5 volts makes the PAN disappear completely In the left lateral position there is a very shortlasting effect and after a few seconds the left beating nystagmus continues with the same intensity despite continuous stimulation

DISCUSSION AND SUMMARY

The visual influences on the nystagmus records in animal is a basic observation which as far as we can see has not been pointed out in the literature In man such observations were made by those who started nystagmography for clinical purposes using the Scott and Meyer technique In a larger clinical material Aschan *et al* (1956*a*) showed that for example the eye speed in the

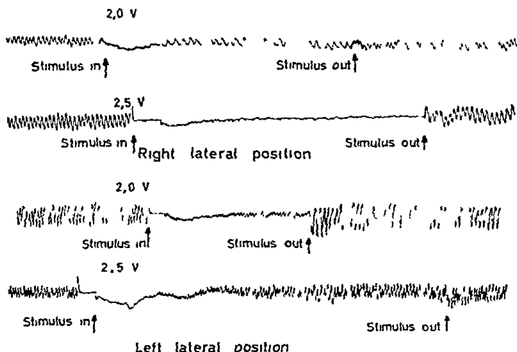


Fig. 11. An electrode point in the nodulus to the right (rabbit 103). Influence of stimulation on PAN. In the right lateral position 2.0 volts decrease the intensity of PAN. 2.5 volts make it disappear as long as stimulation proceeds. In the left lateral position stimulation over the same electrode and with same voltage influences the intensity of PAN but in another way and not so markedly.

slow phase of induced nystagmus was about 5 to 10 times higher in recordings behind closed eyelids than in recordings made under Frenzel's glasses. The duration of calorically and rotatorily induced nystagmus was about 50 to 100 per cent longer when visual influences were eliminated by closed eyelids. Jongkees *et al.* (1962) showed that in a clinical material positional and spontaneous nystagmus was observed much more often behind closed eyelids than when Frenzel's glasses were used. Aschan (1963) stressed these observations. For us it has been of interest to see that these observations in man up till now have proved to be 100 per cent valid for the rabbit too. This has been the case independent of if the nystagmus recorded has its origin in an acute or chronic experimental situation and independent of if the nystagmus has been provoked by rotary stimuli, central lesions, alcohol intoxication and so on. Many of the contradictory results in the literature concerning vestibular physiology and nystagmus might have their explanation in these findings exemplified in Figs. 4, 5 and 6.

Our experiments have shown that if stimulation in the nodulus resulted

in nystagmus this was always influenced by the position whereas the nystagmus provoked by stimulation in the vestibular nuclei was spontaneous by this is meant that it was not influenced by the position of the head

Stimulation in the nodulus resulted in positional nystagmus when the lateral parts of it were stimulated This nystagmus following stimulation was not only influenced by the position but it changed its intensity during continuous stimulation Stimulation in the midline region of the nodulus did not result in nystagmus Stimulation during alcohol intoxication decreased the intensity of PAN ipsilaterally on lateral nodular stimulation and bilaterally on stimulation in the midline region

It seems from our experiments that within such a small part of the cerebellum as the nodulus there must be a very intricate functional organization which must play an important part in the central nervous mechanism behind positional nystagmus

Stimulation in the vestibular nuclei resulted in a spontaneous nystagmus There were areas within these nuclei however which did not respond with nystagmus to stimulation Stimulation within these areas did not influence PAN

From our experiments the impression is gained that within the different vestibular nuclei there is a very complex functional organization Thus stimulation of one region of the triangular nucleus may give rise to nystagmus beating towards the ipsilateral side another region to nystagmus beating towards the contralateral side while other parts may not respond with nystagmus at all This means that each region must be completely covered with electrode points and subsequently examined neuro anatomically before final results can be obtained

From the alcohol experiments demonstrating marked differences when comparing the results from stimulations before during and after alcohol intoxication it may be concluded that the action of alcohol on nystagmus induced by stimulation in the cerebellum and the vestibular nuclei is depressant The observation reported above that stimulation in the nodulus inhibits PAN ipsilaterally and that lesions in the same region cause ipsilateral increase in the intensity of the PAN (Grant Aschan & Ekvall 1964) suggest that an essential factor in the elicitation of PAN may be a depressing effect of alcohol on the nodulus and its connections this effect being partly compensated for during nodular stimulation These conclusions support the postulation of Spiegel & Scala (1942) Dow & Moruzzi (1958) Gernandt & Gilman (1959) and Gernandt (1963) that the cerebellum has an inhibitory effect on vestibular centres

The alcohol experiments give a practical demonstration of how our method may be used for neuro pharmacological experiments concerning the action of drugs on the vestibular system

From our experiments we have found that no definite conclusions can be drawn from stimulation experiments alone The tolerances when implanting electrodes even with a rather good stereotaxic atlas and technique are too

large to allow dependence on alone The neuro anatomical analyses using serial sections have too often shown that seemingly contradictory results in identical implantation experiments have had the rather simple explana tion that different regions have been hit In addition we want to stress that the neuro anatomical analyses with serial sections are necessary for eli minating bleedings abscesses etc as sources of error

With the adopted technique which is however rather complicated and time consuming it will be possible to study the effects concerning nystagmus from stimulation of other parts of the cerebellum and the brain stem than the ones which have been reported here Some experiments have been made with electrode points in the lingula and the uvula in the cerebellum as well as in some reticular nuclei in the brain stem Further experiments will be made before the findings from stimulation in these structures will be re ported

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NYSTAGMUS PRODUCED BY LOCALIZED CEREBELLAR LESIONS

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INTRODUCTION

This study was prompted by results from the investigation that has just been presented by Aschan Stimulation over implanted electrodes with their unisolated points localized in the lateral parts of the nodulus (Larsell's lobulus X) in rabbits resulted in nystagmus It was deemed of interest to make unilateral lesions restricted to the posterior part of the vermis including its vestibular portion (i e the nodulus) and subsequently to examine the animals with regard to nystagmus The aim was to make these unilateral lesions restricted to one lobulus only or to part of a lobulus without causing any damage to the brain stem As regards the nodulus this proved to be very difficult because of its hidden position However, with the technique which was developed during this investigation such lesions will be possible to make Even if thus no cases with pure unilateral nodular lesions are included in the present material the results obtained will be of interest

MATERIAL AND METHODS

From a total of 46 adult pigmented rabbits which were submitted to operations 18 have been used for the present study The animals were anesthetized with a mixture of nembutal–chloralose–urethan (0 2 ml 6 % nembutal + 2 5 ml chloralose (1 %)—urethan (10 %) per kg body weight) given intravenously In addition up to 4 ml 0 5 % xylocain exadrin was injected locally under the skin The animals were placed in an open box and the head was fixed in a holder which permitted the rather pronounced ventroflexion of the head which was necessary during the last part of the operation The operations were performed with sterile precautions An operation microscope (magnifying about × 10) was used during the last part of every operation Bleedings were stopped by thermocoagulation when necessary Great care was taken, however, so as to avoid the deep structures surrounding the central nervous system Saline was used to avoid drying of the nervous tissue The posterior atlanto occipital membrane was exposed by a midline approach Part of the occipital bone covering the posterior vermis was removed outside the dura The dura and arachnoid membranes were opened From here on, the operations have been performed somewhat differently in different cases In eight animals electrolytic lesions were made, and in ten other animals lesions were produced by suction

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For the electrolytic lesions unipolar needle electrodes insulated except for their points were used Those aimed for the nodulus were bent so that they could be introduced beneath the posterior vermis A direct current of 1 2 mA for about 5 to 30 sec was used

For suction cannulas (outward diameter 0 7 mm inward 0 4 mm) connected to a vacuum pump were used The cannula aimed for the nodulus was bent so that it could be introduced beneath the posterior vermis

When the nodulus was aimed to be destructed unilaterally it was originally approached after an incision had been made in the thin roof of the posterior part of the IVth ventricle Since many of the cases in that group had to be omitted because of concomitant lesions in the brain stem when electrolytic lesions were made (spread of current through the liquor[9]) and it proved difficult to come close to the cortical surface with the cannula when that was used a more direct approach was adopted An extremely careful dissection under the microscope made it possible to sever the thin fibres connecting the pia of caudoventral part of the vermis with the posterior part of the roof of the IVth ventricle After such a dissection it was possible to introduce the electrode or the cannula above the roof of the IVth ventricle

The dura was left unsutured The animals were given penicillin intramuscularly after the operation

After the operation and until the animals were killed a period varying from 2 to 36 days they were examined and tested in the way already described by Aschan In summary they were tested with the naked eye as well as with nystagmography with regard to the existence and character of spontaneous or positional nystagmus They were submitted to rotatory tests and alcohol induced positional nystagmus was examined

The animals were killed under nembutal anaesthesia (40 mg/kg body weight) by perfusion with formol saline acacia according to the method described by Koenig Groat & Windle (1945) The central nervous system rostral to the third cervical segment was removed immediately after the perfusion and immersed in neutral formol saline solution (5 %) for at least 3 days The cerebellum was then separated from the rest of the brain Photographs were taken from the cerebellum and sometimes from the brain stem The part of the cerebellum containing the lesion was separated by sagittal sections from the remaining portion of the cerebellum Most of the separated cerebellar blocks containing the lesions were embedded in paraffin and cut in serial sagittal sections at 20 μ Every second section was mounted and stained with thionin The remaining sections were kept mounted but unstained Some cerebellar blocks were cut at the freezing microtome in serial sagittal sections at 20 μ They were collected in groups of 10 From each group one section was mounted and stained with thionin The remaining sections were reserved for being used for a separate study using silver methods for tracing degenerating fibres from the vestibular part of the vermis Most of the brain stems were cut in serial transverse sections at 20 μ at the paraffin microtome The sections were then treated as the corresponding cerebellar ones Some

brain stems have been reserved for the separate study concerning the cerebellofugal fibres from the uvulo-nodular region. However they were all examined carefully under a preparation microscope magnifying about 13 times.

When examining the sections the atlas of the rabbit's cerebellum by Brodal (1940) and the cytoarchitectonic atlas of the rhombencephalon of the rabbit by Meessen & Olszewski (1949) were used.

RESULTS

In none of the cases included in this investigation has there been found any damage to the brain stem, nor to the cerebellar nuclei. The material can be divided into two main groups according to the *anatomical findings*.

The first group is represented by 5 cases with unilateral lesions of the nodulus and the ventral half of the uvula (i. e. lob. a and folia 1 and 2 of lob. b according to Brodal 1940) (Fig. 1). Two of the cases in this group did also show damage to the dorsal half of the uvula (i. e. fol. 4 and 3 of lob. b).

The second group is represented by 6 cases with unilateral lesions of the ventral part of the uvula (i. e. folia 1 and 2 of lob. b according to Brodal 1940) (Fig. 2). In three of the cases in this group the lesions did also encroach upon the dorsal part of the uvula (i. e. folia 4 and 3 of lob. b) and in addition to a small extent they encroached upon the dorsal or upon the caudal part of the nodulus.

In addition to the cases included in the two groups which have just been mentioned, there are two cases with unilateral lesions restricted to lobus c.

Five additional cases with more heterogeneous lesions of the posterior vermis, mostly bilaterally, are included in the material and will be mentioned below.

The cases belonging to the first group, i. e. with unilateral lesions of the nodulus and the ventral portion of the uvula, demonstrated a common pattern regarding *the physiological findings*.

The findings of *rabbit 214* will serve to illustrate this pattern. In this case there was a lesion on the left side of the nodulus and the ventral portion of the uvula. The first day after the operation positional nystagmus was found in the right lateral position. This nystagmus was beating to the left, i. e. to

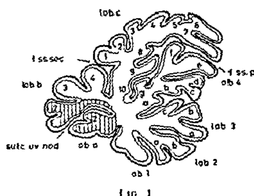


Fig. 1

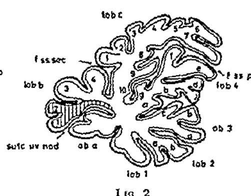


Fig. 2

Figs. 1 and 2. Mid-sagittal sections of the rabbit's cerebellum. Drawings slightly modified after Brodal (1940). Hatched areas indicate sites of lesions in the first and second groups respectively. Compare with text.

Rabbit 222 Right sided uvulo nodular lesion
Not intoxicated
Preponderance to the right in rotatory test

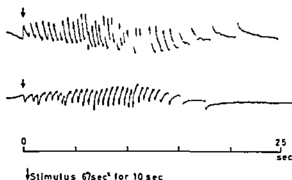


FIG 3 Preponderance to the right in rotatory test The upper trace represents the rotatory answer to acceleration to the right the lower trace the answer to acceleration to the left

wards the side of the lesion The third day after the operation left beating nystagmus was found in the erect position as well as in the right and left lateral positions The fifth day after the operation there was still nystagmus in the three positions mentioned and this was still beating towards the side of the lesion In the lateral positions a vertical component could also be noticed beating towards the upper lid on the right eye and towards the lower lid on the left eye let us call it anticlockwise The third day postoperatively a rotatory test demonstrated directional preponderance to the left (cf Fig 3) The fifth day postoperatively the alcohol induced positional nystagmus was more pronounced towards the left in the left lateral position than the nystagmus towards the right in the right lateral position (cf Fig 4)[1]

To sum up The lesion on the left side produced positional nystagmus This was mainly horizontal beating to the side of the lesion In addition there was a vertical component beating anticlockwise The alcohol induced positional nystagmus was asymmetric beating more pronounced towards the side of the lesion The nystagmus induced by rotation did also show an asymmetric pattern The nystagmus beating towards the side of the lesion was dominating

The findings of rabbits 213 and 223 were essentially the same In rabbits 222 and 224 the operation had been made on the contralateral on the right side A positional nystagmus was produced It was horizontal and contained a vertical component The horizontal nystagmus was beating to the side of the lesion as in the cases with lesions on the left The vertical component however was beating clockwise There was an asymmetry in the alcohol induced positional nystagmus with a dominance for the nystagmus beating to the side of the lesion Rotatory test demonstrated an asymmetry with a dominance for the nystagmus beating to the side of the lesion

[1] In the intact animal alcohol will produce positional nystagmus This will beat to the left in the left lateral position and to the right in the right lateral position

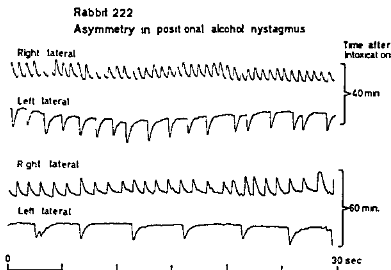


FIG 4 Asymmetry regarding alcohol induced positional nystagmus 40 minutes after intoxication the frequency of the nystagmus beating to the right in the right lateral position clearly dominates over the frequency of the nystagmus beating to the left in the left lateral position An asymmetry is still present 60 minutes after intoxication

The cases belonging to *the second group*, i e with unilateral lesions of the uvula seemed to have a common pattern regarding *the physiological findings*

The findings of *rabbit 202* will serve to illustrate this pattern In this case there was a lesion on the left side of the ventral portion of the uvula with a minor encroachment upon the caudal pole of the nodulus on the same side The second day after the operation no spontaneous or positional nystagmus could be detected The third day after the operation positional nystagmus was present in the right lateral position It was beating to the left i e contrarily to that lateral position in which the animal was placed A rotatory test the same day revealed directional preponderance to the right i e from the side of the lesion The fifth day the left beating positional nystagmus in the right lateral position was still present Moreover nystagmus was present in the left lateral position Here it was also beating in a direction contrarily to that lateral position in which the animal was lying i e to the right The same day the *nystagmus induced by alcohol* was asymmetric It was most pronounced to the right i e from the side of the lesion

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The findings of the remaining five cases belonging to this group (rabbits 195 196 200 220 and 221) were about the same In three of the cases however, with lesions rather close to the mid line, the rotatorily induced as well

as the alcohol induced nystagmus did not show any asymmetry In one of these cases as well as in another case both with small lesions nystagmus was found only in one of the lateral positions Two cases demonstrated vertical components in their positional nystagmus In one of them the lesion did not encroach upon the nodulus

In the two cases with unilateral lesions (one to the right one to the left) restricted to lobus c there was found positional nystagmus beating clockwise

The five cases with more heterogeneous lesions of the posterior vermis together with the cases already reported from above serve to illustrate that an asymmetry revealed by a rotatory test in this material is accompanied by an asymmetry in the alcohol induced positional nystagmus Furthermore a rotatory directional preponderance e g to the right is accompanied by an alcohol positional nystagmus dominating to the same side

Finally some findings which are possibly connected to vestibular mechanisms will be preliminarily reported

The rabbits belonging to the first of the main groups mentioned above i e rabbits with unilateral lesions of the nodulus and the ventral portion of the uvula demonstrated postural asymmetries immediately after the operations before they were fully awake If the cerebellar lesion was localized to the right e g the right forelimb was going up to a pronounced extension when the animal was placed in a supine position with its snout slightly elevated There was an abduction of the forelimb at the same time The right hindlimb was not convincingly extended When the animal was placed in a prone position the right forelimb was extended the head rotated slightly so that the right eye was facing slightly upwards The head was turning slightly to the left giving the impression of a contraction of the sternomastoid muscle of that side

Two of the cases were examined again during light narcosis some days later and the same behavior was shown to be present

DISCUSSION

When trying to explain the effects which have been reported here on the basis of the known fibre connections to and from the regions which have been included in the different lesions there are several difficulties One of these is that the lesions produced probably do not only affect the efferent but also the afferent fibre connections Another difficulty is that there are still gaps in our knowledge concerning e g the efferent fibre connections from the nodulus

From the results obtained from the first main group with unilateral lesions of the nodulus and the ventral portion of the uvula the impression is gained however that a cerebellar inhibition acting on the same side of the brain stem has been abolished The cases belonging to that group showed positional nystagmus beating to the side of the lesion rotatory preponderance to the same side and the alcohol induced positional nystagmus dominated to

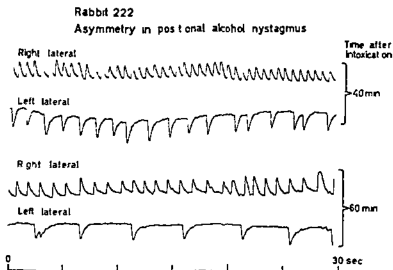


Fig. 4. Asymmetry regarding alcohol induced positional nystagmus. 40 minutes after intoxication the frequency of the nystagmus beating to the right in the right lateral position clearly dominates over the frequency of the nystagmus beating to the left in the left lateral position. An asymmetry is still present 60 minutes after intoxication.

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To sum up: The lesion on the left side produced positional nystagmus. This was horizontal, beating to the left in the right lateral position and to the right in the left lateral position. Alcohol induced positional nystagmus showed an asymmetry, beating more pronounced from the side of the lesion. Nystagmus induced by rotation did also show an asymmetric pattern. The nystagmus beating from the side of the lesion was dominating.

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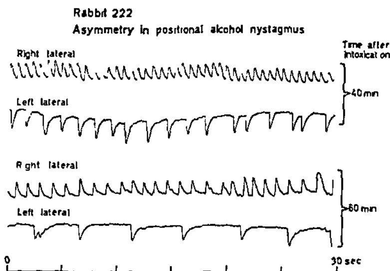


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PHYSIOLOGICAL ASPECTS ON THE STRUCTURE OF VESTIBULAR END ORGANS

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Morphological investigations on the vestibular end organs and on the closely related lateral line canal organs have during the last decade yielded so much information that a correlation of morphology and function on a cellular level is now possible

All mechano receptor epithelia in the labyrinth and the lateral line system basically exhibit the same architecture being composed of sensory cells or hair cells embraced by supporting cells resting on a basement membrane (Figs 1 2) *The receptor cells are provided with sensory hairs* coupled to auxiliary structures which transmit vibratory or gravitational stimuli to the sensory cells The responses of the receptor cell regulate the flow of impulses in the innervating nerve fibers

The vestibular sensory epithelia in mammals are composed of two types of sensory cells type I and type II (Wersäll 1956) (Fig 1) The type I cell is enclosed by a large nerve chalice enclosing the amphora shaped cell, whereas the cylindrical type II cell is innervated by several small nerve endings at the bottom of the cell

The type I hair cell is considered to be the most highly differentiated [illegible] specialized cell whereas the type II cell is more primitive Lateral line organs and labyrinthine organs in fish birds and amphibia contain [illegible] cells resembling type II hair cells (Wersäll & Flock, 1964)

Electron microscopic investigation has revealed that these [illegible] helia contain at least two different types of nerve endings [illegible] content of synaptic vesicles Studies on the localization of [illegible] the vestibular sensory epithelia and the organ of Corti in [illegible] shown that the cholinesterase is closely related to the vesiculated [illegible] (Hilding & Wersäll 1962) It was postulated that these nerve [illegible] be efferent in function (Engström 1958) a theory which [illegible] experimentally approved (Iurato 1962 Kimura & Wersäll [illegible] established that the vestibular sense organs are innervated [illegible] efferent nerve fibers *There is reason to believe* that an [illegible] and efferent impulses governs the function of the organ

Supported in part by the National Institute of Health grant No [illegible]
the Swedish Medical Research Council [illegible]

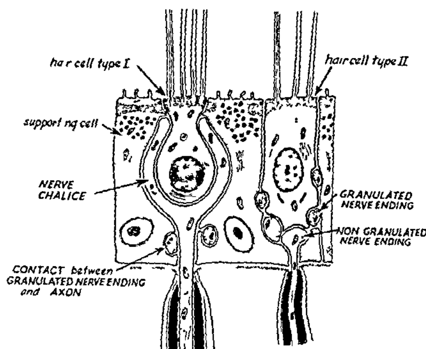


Fig. 1. Schematic drawing of the hair cells in the vestibular sensory epithelium as it appears in cat, guinea pig and rat. (Reprinted from Wersall, 1960, *Neural Mechanisms of the Auditory and Vestibular Systems*.)

The absorption of energy from the associated structures takes place in the hair bearing end of the cell. The sensory hair bundle protruding from the cell surface is composed of 40–70 stereocilia and one kinocilium. The bulk of each stereocilium is formed by densely packed fibrils, about 30 Å in diameter, which converge towards the base of the cilium forming an axial fiber penetrating into the cuticle of the cell. The kinocilium resembles motile cilia being composed of a central pair of fibers surrounded by nine double fibers. It is ensheathed by a plasma membrane which is continuous with the cell membrane. The peripheral fibers of the kinocilium are continuous with the triple fibers of a basal body located in the periphery of the cuticle.

Studies of cross sections of the hair bundles have revealed a consistent arrangement of the sensory hairs. The kinocilia are always located in the periphery of the hair bundle. In the crista ampullaris of the horizontal ampulla the kinocilium is found on the side of the bundle towards the utricle, whereas it is found on the canal side of the cristae in the other canals (Fig. 2). This means that the location of the kinocilium coincides with the direction of excitation of the cell. The morphological polarization of the cell thus reflects its functional polarization (Lowenstein & Wersall, 1959).

The utricular macula exhibits a more complicated pattern of orientation. Emanating from a point in the medial part of the macula the kinocilia are pointing in gradually altering directions from anterior passing lateral to posterior covering approximately a semicircle (Flock, 1964). In a zone along

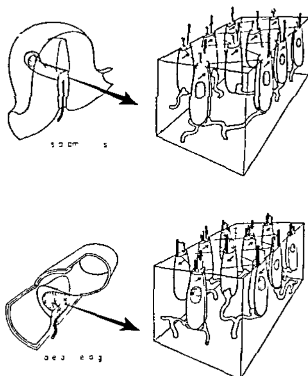


FIG 2 Diagram of the crista ampullaris and the lateral line organ with enlarged areas of the sensory epithelia demonstrating schematically the arrangement of the receptor cells and the orientation of the sensory hair bundles The kinocilium is painted black In the crista ampullaris the kinocilium is always found at the same side of the bundle while in the lateral line organ adjacent hair cells are polarized with the kinocilia pointing in opposite directions The pattern of innervation of the sensory cells is imaginary The cupula overlying the epithelium is omitted in the drawings at higher magnification (*Reprinted from Flock & Wersall 1962 J Cell Biol*)

the anterior lateral and posterior margins of the macula the hair cells are oriented with their *kinocilia pointing in opposite directions*

In the lateral line organ alternating cells are provided with hair bundles with the kinocilium oriented towards the head and alternating cells with the kinocilia oriented towards the tail (Flock & Wersall 1962) (Fig 2)

With these facts in mind it is interesting to note that although the hair cells in the organ of Corti are devoid of a kinocilium they are however provided with a centriole located in the periphery of the cuticle and always facing from the modiolus a location which coincides with the stimulating direction of the outer hair cells (Flock *et al* 1962)

The basic electrophysiological principle in these sense organs is their bidirectional response to stimuli approaching from opposite directions It has been proposed that displacement of the sensory hairs toward the kinocilium is accompanied by depolarization of the cell and increased discharge rate in the innervating nerve fibers (Flock & Wersall 1962) whereas displacement in the opposite direction is accompanied by hyperpolarization

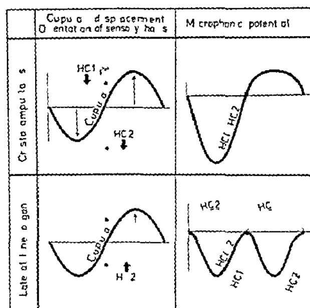


Fig 3 Illustration of the hypotheses of hair cell response to cupular d splacement in two opposite directions applied to the crista ampullaris an l to the lateral line organ In the crista all hair cells are polarized in the same d rection as is indicated by HC 1 an l HC 2 Cupular displacement in th s direction is excitatory for both cells and is followed by a decrease in potential while d splacement in the opposite direction is accompanied by an increase in potential as is shown by the right curve representing the sum of responses from HC 1 and HC 2

In the lateral line organ HC 1 and HC 2 are polarized in opposite directions The potential changes induced by cupular displacement through HC 1 will follow the course indicated by the dotted curve marked HC 1 in the right figure while potential changes evoke l by HC 2 will follow the course indicated by curve HC 2 The recorded microphonic potential represents the sum of these two opposed responses curve HC 1 + HC2 and will consequently show a frequency double that of the cupular displacement (Reprinted from Flock & Wersäll 1962 *J Cell B ol*)

and decreased discharge frequency This theory is consistent with the ori entation in the crista described above It also explains the double frequency of the microphone potential recorded from the lateral line canal organ (Fig 3) The lateral line organ is innervated by two distinct groups of nerve fibers responding to head tailward and tail headward direction of stimulation respectively corresponding to the above mentioned two groups of sensory cells oriented in opposite directions

The microphone potential output from the lateral line canal organ is consequently the sum of two antagonistic responses where in each cell the depolarization must be larger than the hyperpolarization caused by equal displacement in opposite directions otherwise no microphone potential would be recorded (Fig 3)

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EFFERENT AND AFFERENT ACTIVITY PATTERN IN THE VESTIBULAR NERVE OF THE FROG

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The activity was studied in the vestibular nerve of the frog, and was picked up in three different ways I efferent activity from the proximal end of the cut nerve, II afferent activity from the distal end of the cut lateral ampullar nerve, and III impulses travelling in both directions from the intact lateral ampullar nerve

I The efferent activity in the vestibular nerve which takes its origin in the opposite labyrinth at horizontal rotations was studied There was normally no resting activity of efferents but at utriculofugal accelerations (causing utriculofugal cupula deviations in the ampulla of the ipsilateral horizontal canal) a definite response appeared At utriculopetal accelerations the response was, however, much less clear cut and presented a varying pattern

Thresholds at angular accelerations for efferent activity were found to be higher and latencies longer than for afferent activity At repeated stimuli efferent activity showed a varying degree of response decline

Ether applied to the frog s skin caused a transitory abolishment of efferent rotatory response, which when reappearing showed a steeper response decline at repeated stimuli

Ethanol applied in the same way also abolished the efferent response to rotation but initiated a resting efferent (?) activity in the nerve

II Afferent activity was studied for comparison with efferents

III The activity in the intact lateral ampullar nerve revealed efferent activity at utriculofugal accelerations against a background of a total decrease of afferent activity The efferent activity was caused mainly by afferents from the opposite lateral ampulla and could be abolished by ether At utriculopetal accelerations the increase of afferents tended to conceal a possible presence of efferents An analysis of the activity at such stimuli, however, indicated a possible inhibitory effect of efferents on afferent activity

Recent neurophysiology has demonstrated a nervous centrifugal control of many peripheral receptor organs (Granit, 1955, Hagbarth 1960)

In the case of the cochlea such a system is well known and proved both by histological (Rasmussen, 1946) and electrophysiological (Galambos 1956 Fex 1962) technique Efferent fibers reaching the vestibular organ were first

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found with histological methods (Rasmussen & Gacek 1958 Gacek 1960) Also electron microscopy for analysis of the ultrastructural organization of the sensory epithelium of the crista has indicated a double innervation of this structure (Wersall 1956 Engstrom 1958)

Further histochemical methods have supported the concept of efferent activity reaching the labyrinth (Dohlman Farkashidy & Salonna 1958 Rossi & Cortesina 1963)

In his thorough investigation on afferent activity in the vestibular nerve of the frog Ledoux (1958) recorded a change in the resting activity of one side at caloric stimulation of the other This was ascribed to changes of temperature extending from one labyrinth to the other

Until quite recently no efferent activity however had been revealed in the vestibular nerve although hypotheses on the function of an efferent system had been postulated by several authors (Groen 1961 Huur & Mendel 1962)

In February 1963 a paper by Robert S Schmidt appeared claiming efferent activity in the vestibular nerve of the frog Schmidt found efferent impulses reaching most sensory formations in the frog s labyrinth The afferent activity from the contralateral and also ipsilateral ampullae as well as some extra labyrinthine sources seemed to be responsible for the initiation of the centrifugal activity in the lateral ampullar nerve The interaction between the sensory formations was proved by sectioning their nervous connections When Schmidt applied Nembutal to the preparation the efferent activity vanished

For some time we have also in Lund been studying efferent activity in the vestibular nerve of the frog and our attention has been paid to

1 Spontaneous and rotatory efferent response
2 Threshold values of efferents to rotatory stimuli
3 Latencies of efferents to rotatory stimuli
4 Efferent activity at repeated stimuli
5 Blocking effects by ether ethanol and urethane on efferent activity
6 The activity pattern in the intact vestibular nerve carrying impulses in both directions

MATERIALS METHODS AND TYPES OF EXPERIMENTS

Materials

Ordinary frogs (Rana temporaria 15 30 g in weight) were used Pilot experiments on about 150 frogs preceded the present material comprising experiments on 40 frogs

Methods

The frogs were immobilized with intramuscular injections of Tubocurarine Cl (0 5 mg 100 g) or Flaxedil (May & Baker) (6 mg/100 g) They were cautiously pinned on their backs to the operating table and arrangements that could interfere with their normal blood circulation were avoided We also tried to reduce the loss of blood as much as possible The frogs skin was

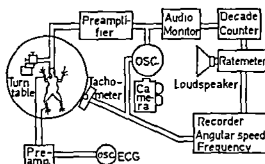


Fig. 1. Block diagram of recording devices.

kept moist and oxygen could be supplied in the trachea intermittently during the operation. One or both eyes were enucleated and the vestibular nerve of one or both sides exposed by carefully removing some bone in the rear of the orbit.

As electrodes were used modified insect pins of stainless steel applied to the nerves with the aid of micromanipulators. The tips of the electrodes were curved in order to make it possible to catch the nerve and lift it from its lodging on the ampulla. Sometimes a thin watchmaker's forceps was used as an electrode.

Fig. 1 presents a block diagram of the electrical recording arrangements. The impulses were visualized on an oscilloscope after having passed an AC coupled preamplifier (Tektronix FM 122, actual frequency range 80–1000 cps), and recorded on a film (Grass C4 J Camera) together with the angular velocity of the turn table. The time constant for the velocity recording (by means of a DC generator) was 20 msec, by sinusoidal movements (15–20 cpm) the phase lag was found to be of the magnitude 10–20 msec between the curve and the real velocity. The delay of the velocity recording at the onset of rotation was, however, found to be of the order 50 μ sec. From the preamplifier the action potentials were also fed to an audiomonitor (Grass) working as power amplifier with adjustable attenuation. In a decade counter (Philips PT 9700) the spikes could then be transformed into uniform pulses and counted. The pulses were integrated in a rate meter (Philips PW 4042) and the pulse frequency was read on a scale and also, synchronously with the angular velocity, recorded on an ink writer (Mingograph, Elema, Sweden) with a time constant negligible at the low frequencies recorded. The time constant for the frequency recording system was 100 msec. The latency between a square wave pulse fed into this system and the rise of the integrated curve on the oscilloscope was about 3 msec. At the sinusoidal movements (15–20 cpm) with the time constants used the frequency curve lagged 50–100 msec behind the velocity curve.

A certain amount of error was, however, introduced into the frequency recording system for the following reasons. At maximal amplification (= attenuation 0) in the audiomonitor part of the background noise (5–15 μV) gave rise to uniform pulses in the decade counter, thus interfering with the biological spike frequency and above all causing a false picture of nervous activity at moments when this activity was very low or totally absent. On the other hand, increase of attenuation in the audiomonitor interfered with the threshold for counting the action potentials of very low amplitude

Further, another possible source of error might be due to changes of electrical resistance in the nerve membranes at different degrees of activity, causing variations of noise level. This might probably be valid only for the lowest range of attenuation.

On the assumption that the noise level and the resting activity in the course of an experiment were essentially stable and the attenuation appropriately chosen, the frequency changes recorded could be expressions for true, biological spike frequency variations dependent on the stimuli given although the numbers of spikes counted (and the frequency figures) were not quite correct.

Film and frequency recording could be used one at a time or simultaneously.

As the experiments were very much dependent on an effective blood supply to the brain, the ECG could be recorded on a separate oscilloscope screen.

For application of vestibular stimuli a turn table was used which could give two kinds of rotatory stimulations. (1) Different constant angular accelerations could be applied by means of falling weights. (2) Sinusoidal clockwise and anticlockwise movements were given by hand. The regularity of this stimulus was checked by the simultaneous recording of the angular velocity.

Types of experiments

The activity in the vestibular nerve was picked up in three different ways furnishing experiments of three different types.

1. From the proximal end of the lateral ampullar nerve or alternatively from the proximal end of the anterior branch of the vestibular nerve cut between the utricular and saccular nerves. In this last case all sensory formations of the labyrinth were destroyed. In the first case the nerve from which recordings were derived was separated from its connections with the peripheral sensory organ.

2. From the lateral ampullar nerve separated from its central connections.

3. From the intact lateral ampullar nerve connected both to the peripheral organ and to the brain.

The accelerations used in the experiments will in this paper be named utriculofugal (UF) or utriculopetal (UP) after the deviation they would cause on the cupula of the lateral ampulla of the side from where the activity is picked up.

RESULTS

1. *Spontaneous and Rotatory Efferent Pattern*

In most of the proximal nerve ending preparations (experiments of type 1) no spontaneous activity could be found, while in a few preparations a sparse spontaneous activity could be seen. Occasionally the preparations also showed irregular bursts of spikes lasting for 2–4 seconds. Sometimes these bursts occurred, however, together with active movements of the frog. Sometimes bursts also appeared when the frog was exposed to rotatory stimuli after having been at rest for some time or when the activity had returned after being blocked by ether.



Fig 2 Efferent activity at sinusoidal rotatory stimulation Recording from the cut proximal end of Ramus anterior N VIII dx. (curare) (Recording from right to left)

In all preparations, however, activity appeared at UF accelerations (Fig 2) In some preparations also UP accelerations caused some response When the opposite lateral ampullar nerve was sectioned most or all of the UF response disappeared, and after paralyzing the whole opposite labyrinth with Xylocain all the activity at the proximal end of the vestibular nerve in most cases vanished The activity abolished by sectioning the opposite vestibular nerve or by paralyzing the opposite labyrinth was regarded as originated by afferents from the opposite labyrinth However, sometimes when recording from the lateral ampullar nerve there appeared impulses even when the opposite labyrinth was paralyzed and these impulses could respond to both kinds of rotations These impulses were interpreted as originated by afferents from other sensory formations in the ipsilateral labyrinth

These findings as well as their interpretations agree well with Schmidt s results

In this series of experiments on efferents in proximal nerve endings with afferents excluded by sectioning the nerve, we tried to establish a centrifugal response to a lateral ampulla evoked by afferents from the same ampulla Thereby we had to record the response from part of the nerve only, in order to allow some afferents to reach the brain for initiating the centrifugal activity As this technique must be expected to interfere with the physiologic generation of efferent activity only few experiments were made to complete our series In one of these we were able to confirm Schmidt s finding of a feed back to the same ampulla

2 *Threshold Values of Efferents to Rotatory Stimuli*

The activity in the proximal end of ... ampullar nerve was picked up in the way ... escri... experi... 1) and the efferent activity recorded during ... nt a ... on ... agnitudes Accelerations of 1° 6° 15°, 2... and ... all accelerations were continued until ... o ... type 2 had shown afferent threshol... e ... t activity, however, seldom if ... d ... as 6°/sec² in spite ... e fact ... e ... elerations of

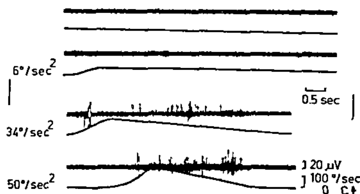


Fig 3 Efferent activity at the proximal end of Ramus anterior N VIII dx at different constant angular accelerations Note shorter latency at 50°/sec² than at 34°/sec² (Flaxe I I) Upper two recordings are continuous (Recordings from right to left)

15°/sec² lasting for 7 sec in most cases initiated efferent activity at least when the stimulus was applied for the first time At repeated accelerations of 15°/sec² the efferent response was not always present At accelerations of the higher magnitudes 21°–50°/sec² efferent activity could almost persistently be evoked provided of course that basic conditions for efferent recording were present

3 Latencies of Efferents to Rotatory Stimuli

Our arrangements for recording of the angular velocity of the turn table synchronously with the impulses in the vestibular nerve and their frequency level were also used for determination of the latencies for efferent activity at different magnitudes of stimulations

Physical properties in the recording arrangements did not allow determinations of latencies shorter than about 100 msec Previous experiments using the present method on afferent activity had shown the impossibility of establishing any latencies Studies on efferents with the same technique and identical experimental conditions showed definite latencies never shorter than 200 msec Frequently especially at low stimuli with short intervals these latencies were much prolonged and sometimes the efferents did not appear until after several seconds

It also seemed as if latencies at accelerations of higher magnitudes were shorter than at accelerations of smaller magnitudes (see Fig 3) The latencies at higher accelerations were also much more constant than those at smaller accelerations (6 21°/sec²)

There was also a great variability both in latency and threshold values as well as in frequency of impulses of the efferent response Thus the close and well defined correlation between stimulus (acceleration × time) and response (frequency of impulses) (Groen Lowenstein & Vendrik 1952) did not seem to be valid for efferent activity

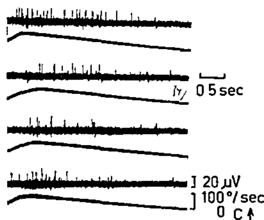


FIG 4 The same preparation as in Fig 3 showing response decline of efferent activity at constant angular accelerations (34°/sec²), repeated at short intervals Slight increase of activity at the last stimulus exemplifies the variability of the phenomenon

4 *Efferent Activity at Repeated Stimulations*

The response decline (RD) of efferent activity was studied using two different kinds of stimuli

1 Continuously repeated constant angular accelerations of different magnitudes 15°, 21°, 34° and 50°/sec² interrupted only by rotations in the opposite direction in order to lift the weight for the next constant acceleration

2 Continuous, sinus shaped, clockwise and anticlockwise rotations with amplitudes of 90° at frequency of 15 20 turns/min These stimuli were applied for up to 10 minutes

When exposed to the first type of stimuli most preparations showed a RD varying in steepness but always present and quite clear cut (see Fig 4) Other preparations showed smaller amount of RD, just indications of it or no definite decline At repetition, the weaker acceleration (15°/sec²) presented the steepest RD while at the highest acceleration (50°/sec²) the RD was less apparent although present In preparations where Flaxedil was used the RD was pronounced

The retention of the acquired RD was indeed very moderate and only 3–5 minutes of rest was as a rule sufficient for the preparations to recover their initial response

Analogous with the previously described finding that higher accelerations caused a more reliable efferent response, sinusoidal accelerations (maximum acceleration about 100°/sec²) provoked a less pronounced decrease of response with repetition of the stimulus Previous experiments on the RD of afferents (preparations type 2) using these stimuli did not exhibit any indication of a RD

5 *Blocking Effects by Ether, Ethanol and Urethane on Efferent Activity*

When a piece of cotton soaked in ether was placed for 6–20 minutes on the belly of the frog the efferent response at rotation was completely or almost

completely abolished Frequently the activity reappeared after times varying between 30 minutes and 1 hour

In many preparations this post ether activity presented a higher incidence of spontaneous bursts as compared to the pre ether activity The reappearing efferents behaved in about the same manner at rotations as before ether was applied but the responses were definitely more apt to decline at repeated stimuli both at constant accelerations and at sinusoidal rotations

In some of these preparations a spontaneous activity lasting for several minutes could be recorded The activity was sometimes of rather low frequency and of a constant amplitude indicating a single fibre firing The rotatory response could be evoked and was recorded on the background of spontaneous activity In one preparation an intense spontaneous activity was present but in this case no rotatory response could be evoked

For control also preparations of type 2 were exposed to ether in an identical manner and the afferent frequency pattern was studied However no change either of the resting activity or of the rotatory response could be ascertained

Efferent activity could also be blocked by application of 2 5 % urethane–water solution on the skin of the frog The efferents then vanished after 3 5 minutes never to reappear even hours after the urethane had been washed away During such experiments the afferent activity was mostly unchanged but sometimes showed a decline possibly due to a peripheral urethane effect The circulation did not seem to be influenced by urethane

In all of six examined frogs 96 % ethanol applied in the same manner for about 15 minutes gave rise to a spontaneous fairly regular activity in the proximal end preparations Sometimes a slight frequency increase could be seen at UP accelerations but mostly no rotatory response could be recorded when the spontaneous efferent activity was at its maximum One frog survived until the spontaneous activity vanished and a rotatory response reappeared After about ½ 1 hour the remaining five preparations showed no activity either in rest or at rotations

6 The Activity Pattern in the Intact Vestibular Nerve Carrying Impulses in both Directions

The arrangements for recording the rotatory stimulus simultaneously with the vestibular impulses and their frequency level together with the possibility for a transitory and selective extinction of efferents by ether made feasible an analysis of the frequency pattern in the intact nerve with and without efferents

A possible change by ether administration of the activity pattern of the whole nerve may be due to

1 A direct peripheral blocking effect by ether on the afferent activity
2 A mere algebraic subtraction or addition of efferent impulses
3 A biological facilitation or inhibition by efferents on the afferent response
4 Combinations of 1 2 and 3

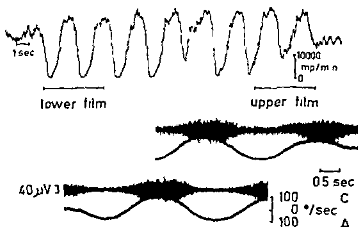


Fig 5 Upper curve Impulse frequency reappearing after ether anesthesia in the intact V ampull lateral sin (preparation type 3) at sinusoidal rotatory stimulation Horizontal bars indicate the time for simultaneous film recordings showing action potentials synchronously with angular velocity of the turn table Note absence of activity in utriculofugal phase after repeated rotatory movements (Recordings from right to left)

The activity in the intact vestibular nerve was studied at constant angular accelerations and clockwise and anticlockwise sinusoidal accelerations

A Before application of ether

Although the frequency level increased at UP and decreased at UF accelerations in roughly the same way as a peripheral preparation of type 2 would do there was an apparent and conspicuous difference at UF accelerations The impulses never quite disappeared at UF accelerations as in peripheral preparations no matter how strong stimuli were used as there was also some activity at those accelerations This was revealed also by the recorded frequency level which was always above the noise or zero level as controlled on the film

B Under influence of ether

When the frogs had been exposed to ether for 6–20 minutes the resting activity did not show any definite change The activity previously remaining at UF acceleration at this stimulus had totally disappeared and the corresponding frequency level had also dropped to the zero level

As efferents appeared at UF accelerations in the proximal nerve endings (experiments of type 1) and as these also disappeared at ether application the activity at UF accelerations was interpreted as being of efferent origin

After ether application there was at UP accelerations no consistent change ... either on the film or on the frequency recording In some prepara...
... level at UP stimulus reached a higher peak level in a few ... most of the experiments about the same values as before ether

This lack of consistent change of UP response after application of ether can be interpreted along different lines and will be discussed later

C *After ether*

Only in one preparation could any indication of reappearing efferent activity be seen In that single case however there was even an increase of activity at UP and UF accelerations compared to that before ether was applied The resting activity remained at about the same level during the whole experiment

After one or two turns of sinusoidal rotatory stimulations the impulses at UF accelerations disappeared and the frequency level dropped again to the zero line (see Fig 5)

At UP accelerations the frequency recording disclosed a decrease of the previous peak values Now apparently the efferent activity was so prone to response decline that a few turns were sufficient to abolish all efferent activity This finding is quite in analogy with the behaviour of efferents reappearing after ether application in proximal nerve end recordings This activity also vanished after a few sinusoidal turns

DISCUSSION AND CONCLUSION

From the findings just presented conclusions about efferent behaviour in normal conditions must be drawn very carefully The main reason for this is that multisynaptic chains might be involved in the generation and transmission of efferent response and such chains are most likely to be influenced also by small doses of the agents used to immobilize the frog Thus although *the mere existence of efferents to the vestibular nerve must be regarded* as proved the quantitative analysis of efferent response can only give hints of a possible physiological pattern

A certain variation in the behaviour of the centrifugal systems of different frogs can thus be explained by the sensitivity of the efferent reflex system to different local concentrations of the agents applied as well as to a changing degree of anoxia

Our efforts to exclude drugs from our experiments by immobilizing the frogs by pithing them have hitherto proved fruitless as no efferent activity could be recorded with such technique

In spite of the relatively small number of experiments where efferent activity could be recorded and in spite also of a certain variation in efferent behaviour we were soon able to recognize the general trend in efferent pattern during the course of our experiment Also in each type of experiment we could soon more or less accurately predict the efferent response

In this investigation was studied efferent activity evoked by horizontal rotatory stimulation its relation to afferents in the lateral ampullar nerve and an interplay between activity in lateral ampullar nerves of both sides The increase of afferent activity in one of the nerves caused by UP acceleration

was found to initiate an efferent outflow to the contralateral labyrinth which agrees with Schmidt's results

As a rule however resting efferent activity in the ampullar nerve separated from its ampulla could not be found but occasionally appeared as bursts of irregular frequency In nerves connected to both the lateral ampulla and the brain there was no change in resting activity after ether application which would indicate that no or little resting efferent activity was present If this failing of resting activity is not an expression of a possible blocking effect by the curare it could be interpreted along the lines of the postulated efferent function According to the postulations efferents would not exert their function until a stimulus of a certain level was reached and would then help to modify effects of too high stimuli

A prolongation of latencies as well as an increase of thresholds for efferent *responses compared to afferents were found in all preparations Also these* findings could however be attributed to a pharmacological blocking of transmission in multisynaptic chains This finding again is in good agreement with the postulated mechanism of efferents evoked only by stimuli of higher magnitudes with the assumed effect of controlling the afferent response

Also the decline of efferent response caused by repeated stimuli may at last be interpreted as a pharmacological effect Suppose that the agents administered for immobilizing the frogs have some blocking effect which decreases the transmission in the reflex chain prolongs the latencies and raises the thresholds it may be assumed that such chains will not release (regenerate) transmittor substances as fast as normally resulting in a RD Further when in a few experiments Flaxedil was used the RD was more pronounced than when tubocurarine was administered

Until the opposite is proved the RD should therefore be interpreted as a pharmacotoxic effect This is even more justified when we take into consideration the steep RD of efferents just reappearing after being abolished by ether The steepness of RD seems thus influenced by the degree of pharmacological effect So in spite of our finding of a decreasing efferent activity at repeated rotatory stimuli it is not unlikely that under physiological conditions efferents do not present any RD In fact the hypothesis of Fluur and Mendel (1962) that efferents increase at repeated stimuli in order to diminish afferent inflow may very well turn out to be true

The aim of the present paper was also to study the activity in the intact vestibular nerve carrying impulses in both directions in order to record its reactivity pattern at different rotatory stimuli but above all to see how this was changed by abolishing efferents with ether

The presence of efferents at UF accelerations was clearly revealed because the afferent activity at these stimuli vanishes leaving the efferent activity alone on the oscilloscope screen The efferent origin of this activity was made probable as the efferents readily disappeared at ether application in accordance with efferent pattern in proximal nerve endings The fact that all or almost all UF phase efferent activity *in these experiments vanished also by sectioning*

the contralateral lateral ampullar nerve tells us that no efferent impulses seem to be evoked by decrease of afferent activity from the ipsilateral lateral ampulla

As to the efferent activity at UP stimuli the results are more difficult to analyse as the afferent activity increases and will thus tend to conceal a possible presence of efferents The interpretation is further hampered by the varying effect of application of ether According to our results the following possibilities must be taken into account

A *No or few efferents are present in the UP response before ether*

The variation would then be due to spontaneous changes of afferent responses or to influence by ether on afferents though both alternatives were unlikely on the bases of earlier experiments

B *Efferents are present in the UP response before ether*

(*a*) *Ether does not influence the efferents* The recording at the proximal end of the vestibular nerve (see Fig 2) clearly showed that the main efferent response was achieved at UF accelerations and that little or irregular response appeared at UP accelerations The main UP efferent response was initiated by afferents from the ipsilateral lateral ampulla (as revealed at recording from the proximal end of the partly cut lateral ampullar nerve) Our criterion that ether abolishes efferents at the intact nerve preparations is valid for the UF accelerations but we do not know if the doses necessary for this also totally abolish efferents caused by UP stimuli Possibly these efferents are less sensitive as fewer neurons might be involved in their reflex arcs This might explain the relatively small changes of UP frequency values under ether influence hardly however the different directions of changes recorded We dare exclude the possibility of ether depression afferent activity if efferents are not quite abolished

(*b*) *Ether does abolish efferents* The variations might also be explained if in different preparations there is a variation in the effect of efferents on afferent response before ether application Nothing is known about the conditions necessary for a normal functioning of the postulated hypothetical inhibition exerted by efferents It is possible that operation trauma disturbed peripheral circulation or even the presence of curare derivatives can damage this mechanism

The few preparations showing decrease of UP peak values recorded after ether application might then be expressions of a mere loss of efferent activity leaving the afferents unchanged The efferents in this case would have had no inhibitory function even before ether The decrease in activity after ether could also be due to afferents depressed by ether but this is improbable as said before

If the assumption is correct that UP stimuli provoke efferents which are abolished by ether then the equal and above all the higher UP frequency values under ether influence might be explained by a loss of efferent inhibitory

function causing a release of afferent activity. This release of afferents will then compensate for, or in some cases even exceed, the loss of efferents caused by ether.

Thus we have hitherto been unable to show any significant effect of the efferent activity, but the results might be compatible with previously presented views on peripheral inhibition by efferents.

The reciprocal innervation of the two labyrinths might help to elucidate findings and phenomena within the vestibular field not yet quite explained.

The vestibular imbalance still present many years after a unilateral loss of labyrinthine function could possibly be attributed to a deficiency in the efferent modulating system besides the effect of a unilateral loss of afferent impulses.

Further, in 1961 it was reported that repeated monoaural calorization caused a response decline found also in the non-irrigated ear, provided that this test stimulus provoked nystagmus in the same direction as the preceding repetitive tests (Henriksson, Kohut & Fernández) The existence of nervous connections between the labyrinths might be taken into account when explaining the mechanism for this transfer of habituation to equivalent stimuli

The abolishment of rotatory efferent response by ether, ethanol and urethane should probably be regarded as expressions of blocking effects in the brain stem, which is known to hold also for other kinds of centrifugal impulses The release of probable efferent spontaneous activity by ethanol and sometimes by ether is more difficult to interpret but might be the results of other and more complicated changes of activity in the CNS At present, these findings are being further studied and analysed and will be published elsewhere

ZUSAMMENFASSUNG

Die Aktivitat im N vestibularis des Frosches wurde untersucht und auf drei verschiedene Weisen registriert I efferente Aktivitat vom proximalen Ende des *überschnittenen Nervens, II afferente Aktivitat vom distalen Ende des überschnittenen* lateralen Ampullennervens und III Impulse, die sich in beide Richtungen des intakten lateralen Ampullennervens fortbewegen

I Die efferente Aktivitat im N vestibularis, die ihren Ursprung im entgegengesetzten Labyrinth bei horizontaler Rotation hat, wurde untersucht Normal war keine Ruheaktivitat von efferenten Impulsen vorhanden, aber bei utriculofugalen Beschleunigungen (die utriculofugale Abweichungen der Cupula in der Ampulle des gleichseitigen horizontalen Bogenganges hervorrufen) trat eine eindeutige Antwort auf Bei utriculopetalen Beschleunigungen war die Reaktion jedoch viel weniger deutlich und zeigte ein wechselndes Bild

Die Schwellen für efferente Aktivitat bei Winkelbeschleunigungen erwiesen sich höher und die Latenzzeiten langer als für afferente Aktivitat Bei wiederholten Reizungen zeigte die efferente Aktivitat einen wechselnden Grad von Reaktionsabnahme

Äther auf der Haut des Frosches brachte die efferente rotatorische Antwort vorübergehend zum Verschwinden Diese zeigte beim Wiederauftreten einen steileren Reaktionsabfall bei wiederholten Reizungen

Äthylalkohol, auf die gleiche Weise zugeführt, brachte auch die efferente Antwort auf Rotation zum Verschwinden, verursachte aber eine efferente (?) Ruheaktivität im Nerven

II Afferente Aktivität wurde zum Vergleich mit efferenter untersucht

III Die Aktivität im intakten lateralen Ampullennerven zeigte efferente Impulse bei utriculofugalen Beschleunigungen, gleichzeitig mit vollständiger Abnahme afferenter Aktivität Die efferente Aktivität wurde hauptsächlich durch afferente Impulse von der entgegengesetzten lateralen Ampulle hervorgerufen und konnte durch Äther zum Verschwinden gebracht werden Bei utriculopetalen Beschleunigungen führte die Zunahme afferenter Impulse dazu, eine eventuelle Gegenwart efferenter Aktivität zu verdecken Jedoch deutete eine Analyse der Aktivität bei solchen Reizungen die Möglichkeit eines hemmenden Effektes von efferenter auf afferente Aktivität an.

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OBSERVATIONS UPON THE NEUROLOGICAL MECHANISM OF SPONTANEOUS NYSTAGMUS IN SUBJECTS WITH UNILATERAL TUMORS OF THE VIII NERVE

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A study has been made of spontaneous nystagmus in 90 subjects with unilateral neurofibroma of the VIII Nerve.

The electronystagmographic characteristics of the nystagmus are described and contrasted with those of the spontaneous nystagmus which results from unilateral section of the VIII Nerve.

An explanation of its neurological mechanism is suggested based upon the effect of the tumor upon the vestibular nuclei and their cerebellar afferents.

SURGERY IN THE TREATMENT OF MENIERE S DISEASE

TERENCE CAWTHORNE
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Today I would like to tell you of my experiences in the surgical treatment of Meniere s disease and to add some comments on recent developments in this field

Dr Crockett of Boston Massachusetts was the first to describe removal of the stapes for vertigo He reported two patients who were submitted to this operation both undoubtedly had Meniere s disease, and both were cured by removal of the stapes This was in 1903

Bearing in mind the fact that these operations were carried out without the benefit of magnification and possibly also without the brilliant illumination to which we are now accustomed it is quite likely that in removing the stapes the utricle or some other part of the membranous labyrinth was avulsed or at least torn open

I say this because in my experience of the surgical treatment of Meniere s disease removal of the stapes alone without opening one of the membranous sacs or tubes does not result in total loss of VIIIth nerve function Neither as I have found does making an opening in the bony lateral semicircular canal without disturbing the membranous tube in fact in one such patient on whom I carried out this procedure the result was somewhat disturbing as exposure to loud sounds was followed by a sharp bout of vertigo in other words the Tullio phenomenon

One might well wonder why fenestration did not result in the Tullio phenomenon and I have shown that this interesting but disturbing effect needs a mobile stapes for its production The reason is that two mobile windows in the bony labyrinth on the vestibular side of the basilar membrane encourages a vestibular response to a cochlear stimulus

Within a year of Crockett s paper Lake of London in 1904, reported operating on the bony labyrinth for vertigo and a year after this Milligan of Manchester also discussed the place of bony labyrinthectomy in the treatment of Meniere s disease Ballance of London in 1919 and Mollison of London in 1931 injected alcohol into the labyrinth which resulted in total loss of VIIIth nerve function on the operated side Between these two dates Georges Portmann in 1928 came out with what in the light of our present knowledge of the pathology of Meniere s disease was the logical procedure namely drainage of the endolymphatic sac However this was not taken up generally possibly because those who tried it were not always sure whether they had opened the endolymphatic sac or the subarachnoid space

I remember how pleased Professor Portmann was when I described at a meeting of the Collegium in 1948 how a patient on whom I had carried out

this operation subsequently became a pilot in the Royal Air Force during World War II Stirk Adams in 1938 then Flett of Derby in 1947 gave their experiences in draining the endolymphatic sac in a series of patients suffering from Meniere s disease

Draining of the endolymphatic sac still is not generally adopted the feeling being that any opening in the sac would soon close with the result that scar tissue would make the wall of the sac even less permeable than usual with a return of the endolymphatic hydrops which is the cause of the symptoms in Meniere s disease Then the young and fertile mind of William House conceived the idea of placing a plastic drain between the endolymphatic sac and the subarachnoid space and with a superb technique using magnification he has done this with success in a series of patients He now finds that in early cases where the hearing losses on the affected side are not greater than 50 db not only does the vertigo disappear but the hearing also improves

When the hearing loss is greater he finds that there is rarely any improvement in the hearing I have seen both Dr House and Dr Sheehy perform this operation and the patient on whom Dr House operated in London has been free from vertigo ever since though the hearing loss which was severe has remained To date I have done twelve of these operations within the past nine months with relief from vertigo in ten

Now to me this seems to be the direction in which one s surgical thoughts should be directed It offers relief from recurrent bouts of overdistension of the endolymphatic system without destruction of VIIIth nerve function and this I believe is the nearest approach to an ideal solution to this difficult problem that we have yet been offered Possibly modification of the procedure described by William House in 1961 will emerge but drainage of the endolymphatic sac by one means or another as originally advocated by Portmann is to me the best thing yet I still think that there is a place for destructive procedures when the disease is unilateral and when the hearing is reduced to a distorted remnant which no patient will thank you for saving as many of us have found

The problems with destructive procedures are (*a*) can they be employed without harm to surrounding structures and (*b*) what happens if the opposite ear becomes affected by the same process? To answer the latter question first Hewlett and I found in 1954 that in a series of 900 cases of Meniere s disease 12 per cent were bilateral however of these half were bilateral from the word go so that in a unilateral case the chance of the other ear s becoming affected was 6 per cent Some of the cases we reported had been under observation for only a year so perhaps it would be safer to say that not more than 10 per cent are likely to become bilateral Recently Bergstedt and Gejrot have reported a series of patients with Meniere s disease submitted to labyrinthectomy in which there was no recurrence of symptoms over a period of 6½ years

Of course when it happens that the second ear is affected after a laby

rinthectomy the patient is in an awkward plight—but this is no worse than if he had been allowed to continue with troublesome attacks from a badly disorganised ear so you see why I still think there is a place for destruction in certain cases

The next part of the question is how should this destruction be carried out? At this stage may I repeat a warning which I gave some years ago Do not introduce into the anatomically crowded area of the petrous temporal bone potent agents of tissue destruction whose effects may spread beyond the target at which they are aimed

Alcohol effective though it is can as many of us know cause trouble Diathermy can also do more than is intended and now we have ultrasound

Arslan introduced the application of ultrasound to the labyrinth in cases of Meniere s disease in 1953 He found that he was able to subdue if not always *to abolish vestibular function by the application of ultrasonic waves* to the lateral semicircular canal in Meniere s disease without destroying hearing There can be no doubt that this is true and the reason for it is that the ultrasonic wave can destroy those vestibular end organs which it reaches without opening the endolymphatic system

I have found that in Meniere s disease it is necessary only to make a tear in the endolymphatic system (or membranous canal or the utricle) for all VIIIth nerve function to be lost

I used to remove the lateral membranous semicircular canal (Cawthorne I operation) but now prefer to remove the utricle via the oval window using the intact stapes to close off the oval window after removal of the utricle (Cawthorne II operation) By avoiding a breach of the endolymphatic system cochlear function may be saved One question which may be asked is whether it is always worth saving Another is can ultrasound reach all the vestibular end organs without affecting important structures such as for instance the facial nerve A glance at the disposition of the facial nerve as it winds around the bony labyrinth reveals some of the difficulties facing those who try to direct an ultrasonic beam so that it affects only the vestibular end organs

In this connection I pay tribute not only to Arslan who introduced this method but also to Angell James and his co workers who have and are doing so much to improve the technique and the application of this daring method I say daring because even with the most refined equipment it is still difficult to ensure that the ultrasonic beam will exert its destructive effect only upon the vestibular end organs Until this desirable end can be achieved I think that the use of ultrasound in the treatment of Meniere s disease should remain in the hands of those who are making a special study of this form of treatment

It may be asked whether this is a surgical procedure but of course it is for the bony capsule of the labyrinth not only must be bared but also must be thinned down before the ultrasonic beam can be successfully applied to the labyrinth Sjoberg Stahle Johnson and Sahl in a thoughtful mono

graph have developed a special ultrasonic generator with a fine applicator which can be kept steady in a groove above the lateral semicircular canal. They report good results with very few complications.

One can but hope that a stereotactic technique similar to that used by the neuro-surgeon will eventually be developed so that one can be certain exactly where the ultrasonic beam will exert its destructive effect. Until that comes about I shall be content to leave this method to more courageous and able hands than mine. Without proper fixation I believe that it is difficult to keep the ultrasonic gun immobile for a matter of minutes. Any slight deflection of the "gun" away from the target may direct the destructive beam upon structures which should not be harmed.

In conclusion may I say that until we know the cause of Menière's disease many sufferers can be relieved only by destruction of the offending end organ. When the disease is unilateral and function is badly disorganised then simple destruction by removal of part of the offending organ is both simple and safe. In early cases where the hearing on the affected side is still comparatively good, drainage of the endolymphatic sac offers great promise and in skilled hands may well prove to be the procedure of choice.

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MEDICAL TREATMENT OF MENIERE'S DISEASE

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It is not an easy thing to read a paper on a subject which formally speaking could be settled in one sentence there is no medical treatment of Meniere's disease And I think it is very important to state this explicitly since only from this starting point we can really try to treat and to cure *patients* suffering from Meniere's disease

We know a lot more about Meniere's disease and its symptoms than a century ago when its namegiver described it so wonderfully In my opinion the way in which this great French master has expressed himself about this subject has never been equalled and surely not surpassed Nevertheless the symptoms are better defined nowadays and something more is known about the anatomo pathology

As we all know Meniere's disease is a clinical entity Patients suffering from it are seized by attacks of vertigo often but not always preceded by vague warnings which enable the patients to sit or lie down before they are knocked down by the attack The symptoms of vertigo vomiting and all the other signs of dysfunction of the inner ear are too well known to go into them here After the attack the patients seem to be well again but for the permanent damage to hearing—a hearing loss of the inner ear type with equal loss of air and bone conduction and with recruitment Many well documented post mortem examinations have left no doubt as to the importance of the inner ear for the occurrence of the seizures

Some things however are not always kept in mind We may know that hydrops of the labyrinth is the anatomo pathological substratum of Meniere's disease but we do not know what brings about the hydrops Quix already found a long time ago that patients suffering from attacks of Meniere very often show a lowering of the corneal reflex on the side of the diseased labyrinth and others have often observed indications that the labyrinthine symptoms do not always fit into a pattern of a pure peripheral lesion

There is still another argument which I believe to be very important for discussion of the treatment of these patients The nervous condition of a patient suffering from Meniere's disease is strongly affected by the fact that he may get into the frightful state of an attack of vertigo at any moment maybe now maybe after some hours days or months This is the reason why those sufferers are often misjudged by people who do not understand the enormous influence of the terror of the next attack when all of a sudden the security of equilibrium will escape them in that agony of having lost the feeling of firm ground of swaying in a vacuum The psychical reactions are not due to an abnormal psychic condition but are a sequel of the disease

On the other hand it is quite sure that the psychical condition is a fertile soil for the disease to prosper.

I am sure that treatment of these patients should commence from this point, i.e. their fright must be taken away by giving them confidence in their doctor. The doctor who is sure about himself, about the treatment he is giving the patient, will have the best chance to make his patient trust him. This is the reason why some doctors use treatments with striking success which have no results in the hands of others. The use of prismatic spectacles is, I think, a typical example. Those who really believe in this treatment cure their patient, those who do not share their faith, have no success.

The fact that this strong psychic influence is present, proves that there are circumstances, *dependent upon the psychical condition of the patient,* which are of the greatest importance for the possibility to cure the sufferers from Menière's disease.

I am afraid that I myself am an incurable unbeliever as regards many theories about the origin of Menière's disease. I am not convinced that hydrops labyrinthi depends upon disturbed water or salt metabolism, allergy, tonus differences in the centres of eye muscles, or so many other things brought forward by those who successfully treat these patients according to their theory. As so many psychic influences seem to find their way towards somatic deviations via the condition of the vessels, I may follow those who try to influence Menière's disease by provoking hyperaemia, either locally or generally.

Personally I think the first step in treating a patient, suffering from Menière's disease is the examination. The doctor has to show the patient that he is interested. The anamnesis has to be very thorough, not only to exclude all those other ailments which may cause spells of vertigo, but also to show the patient that his complaints are taken seriously, that *he* is taken seriously. *Too often the doctor hears the word vertigo and has his prescription ready* without giving the patient the opportunity to free his soul from the many things which oppress him. It is inadmissible not to examine the patient very thoroughly, because this is the only way to really gain his confidence, the basis for all treatment. I remember quite well the many patients who, after a thorough examination in the torture chamber of the vestibular department, told me that they felt much better already since we had been able to cause in them artificially sensations equal to those they felt during an attack of vertigo and many of you have surely had the same experience.

This is the point from which to start treatment. First of all the patient should be brought back to normal life as much as possible. A great many of our patients, having a sedentary life already, eating, smoking and drinking too much already, having too little bodily exercise and living under too great a strain already, get only worse as soon as the vertigo attacks start. They hardly dare to go out, grow fatter, smoke and drink more and live under a greater strain as a result of the psychic condition brought about by their complaints.

The patient must be brought to return to a normal life, often a life much

more normal than the one he lived before the first signs of his trouble began to show. He should be induced to take bodily exercise—walking, swimming, playing golf or all such sports that have no element of personal competition in it. He should eat lots of vegetables and fruit and take care lest he grows too fat. Smoking and drinking should not be excessive. A holiday away from work, household or other responsibilities or strain is mostly of paramount importance to start a successful treatment, at least if the patient can abstain from the modern way of spending holidays by consuming miles, climbing mountains or such things and in that way nearly killing himself so that he can only save his life by quickly returning to routine work. For those who can afford it a sea voyage sometimes works miracles. Surely the doctor should take care that this patient sleeps well. If necessary he should not be too reluctant in giving soporifics. It may also be necessary to help the patient to fight his nervous tension by giving him sedatives. I must confess I prefer the older type—bromine salts, valerian and such like—to the new drugs, which are so effective in various other respects.

If the treatment of the Menière patient starts with these general measures it is possible to spare the patient and the doctor a great many disappointments. In many cases they will be enough to cure the patient from his trouble and in many other cases a treatment directed against the pathologic condition of the inner ear will have a much better chance now.

I think to be able to prove this statement by the fact that in the course of some 25 years I have been obliged to destroy a labyrinth by operation in only 9 patients on account of incurable Menière's disease. All the others, and there were hundreds of them, responded to medical treatment, be it that this treatment asks a lot of confidence, patience and persistance from both patient and doctor.

As I stated above, I feel sure that many ways may lead to success provided the doctor believes in them and is able to make the patient believe in them. *Saltfree diet, prismatic glasses, exercises, urotropine, nicotinic acid* and many others sometimes give excellent results.

In my hands—perhaps because I believe in the experiments which have clearly shown the effect it has on labyrinthine reflexes in both rabbits and human beings—cinnarizine gives the best results. Cinnarizine strongly suppresses the effect of vestibular stimulation.

Philipszoon has demonstrated the effect both for the reflexes originating from the semicircular canals and from the otoliths.

It is a good thing we do not depend any longer on the opinion of the patient only in order to judge the effect of drugs upon vertigo and esp. on vertigo in Menière's disease. Since we use electronystagmography as a routine to examine patients suffering from Menière's disease we know that the statement that in between attacks the patient is free from spontaneous vestibular symptoms is generally untenable. As long as the trouble is still active, as long as the danger to be subject to vertigo is still present the patient shows spontaneous nystagmus or positional nystagmus to a larger than normal extent.

By E.N.G. we could establish the fact that cinnarizine has a strong influence on vestibular disorders in patients suffering from Menière's disease. Not only "cinnarizine in our hands" but cinnarizine all alone. In double blind experiments performed by Philipszoon this was made highly probable statistically, as the outcome was very significant

Since the time we use cinnarizine (3 times daily 40 mg) we have hardly ever had to resort to other medical or, *a fortiori*, surgical treatments.

If the patients do not respond to the above described general treatment combined with cinnarizine we always hospitalize the patient in order to make more sure that we have not overlooked some underlying cause for a symptomatic morbus Menière. If this is not the case we sometimes get good results from blocking the stellate ganglion according to Garnett Passe or from intravenous infusion of histamine solution. Only after a failure of this treatment we eventually resort to destruction of the labyrinth either by Arslan's ultrasonic rays or by Cawthorne's technique.

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INTRAVENOUS INJECTION OF 7% SOLUTION OF SODIUM BICARBONATE FOR THE TREATMENT OF MENIERE'S DISEASE

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Intravenous injection of sodium bicarbonate solution is not a symptomatic therapy but an essential therapy for Meniere's disease For the explanation of this therapy therefore reference should be made to the problem of what the entity of Meniere's disease is However at present we know only little about the entity of Meniere's disease

Autopsy finding of labyrinthine hydrops has long attracted attention as a pathological change occurred in Meniere's disease and the etiology has been sought by many in the mechanism involved in the pathological change of labyrinthine hydrops Among a variety of theories upon the mechanism Kobrak's theory of circulatory disturbance in the inner ear has been widely accepted of late

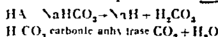
Quite possibly the red exudate in semicircular canals reported by Meniere was the result of the circulatory disturbance in the inner ear

This circulatory disturbance is the so called angioneurosis O Muller described the changes as anemia and oxygen deficiency in capillaries due to the contraction of arterioles followed by flask like inflation of capillaries resulted from the damage to the endothelia and finally edema and diapedese bleeding in the surrounding tissue *Therefore angioneurosis in the inner ear* quite probably produces labyrinthine hydrops and diapedese bleeding

The effect of intravenous injection of sodium bicarbonate solution can be explained in terms of the relief of the angioneurosis relief of arteriole contraction better oxygen supply and faster absorption of edema This idea is justified by the following experimental observations

In rabbits elevated blood pressure due to the vasoconstrictive action of the injected barium chloride returned to normal immediately after the injection of sodium bicarbonate Also the previously lowered oxygen tension in the inner ear of guinea pigs was raised back to normal value by the injection of the solution The absorption of the bullae which was made intradermally with normal saline was accelerated by the injection of the solution

Then how does the intravenously injected solution of sodium bicarbonate act Our present understanding is that acid metabolites accumulated in the involved tissue are neutralized with sodium bicarbonate and that carbon dioxide released alleviates the contraction of arterioles This can be formulated as follows with acid metabolites represented as HA



$$HA + NaHCO_3 \rightarrow NaA + H_2CO_3$$
$$H_2CO_3 \xrightarrow{\text{carbonic anhydrase}} CO_2 + H_2O$$

The elevation of specific viscosity of blood which obviously takes a part in the circulatory disturbance in angioneurotic condition is reduced by sodium bicarbonate resulting in the better absorption of local edema.

With the equally important buffer effect upon the various chemical reactions in the blood sodium bicarbonate helps to restore the impaired balance of metabolism in the tissue. Thus intravenous injection of sodium bicarbonate very effectively controls the attacks of Ménière's disease.

Clinically 7% solution is injected into a cubital vein usually 50 cc at a time but infusion of 150 cc for a severe or a persistent case. The fact that there is no side effect of the therapy may be accounted for by the character of the substance as a buffer substance. Nephropathy does not significantly retard the excretion of excess amount of sodium. In Japan 7% solution of sodium bicarbonate is widely used as an official medicine approved by the National Health Insurance Organization.

HEARING TESTS IN MENIERE'S DISEASE

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Last year's literature relating to hearing tests in Meniere's disease adds little to what we have known for some decades, and little research has been done on this subject. This is perhaps easy to understand: one might draw a parallel with otitis, where it is not the defective hearing that is the chief concern in the acute stage but rather the pain, temperature and other manifestations. In Meniere's disease it is, of course, the attacks of vertigo that are the dominating feature. One need not be a psychologist to understand why the hearing symptoms remain unnoticed and then neglected until difficulty arises in communicating with the immediate environment, and then we are already down to the familiar 40 db level according to the British and European standard and the 30 db level according to the American. In the case of vertigo, on the other hand, from the very outset the person feels that there is something seriously wrong, and he consults a doctor, perhaps even before the attack has developed fully. In contrast to this subjective evaluation of the initial stage and the development of the first years in a typical case of Meniere's disease are the final stage and the factors that may lead to invalidization. We are well aware that the young case, at least, can easily go on living with a vestibular loss even when it is almost total and bilateral. There is a general compensation that is so nearly complete that the patient himself is unaware of the severity of his condition and the doctor, too, overlooks it. For instance, in this country there must be some 50 motorists with no vestibular reaction at all who, as far as I can hear, drive just as well as, if not better than, we who are sitting here.

On the other hand, there are those steadily deteriorating symptoms in the form of deafness and the extremely troublesome tinnitus that can be properly evaluated only by the sufferer himself. It will therefore also be the state of the hearing that will determine whether or not surgical measures are indicated: it is the hearing that we must save, cost what it may.

In hearing tests the sentence is always justified that no chain is stronger than its weakest link. I am not thinking of the ossicular chain, which constitutes in fact only one of the links. The chain begins with the person that performs the hearing test, and it cannot be stressed too much that this person shall be quite conversant with

(i) the do's and don'ts of the measuring technique,
(ii) the sources of error and how they can be avoided, and
(iii) the art of making personal contact with the patient.

It is not my intention to draw any comparison with the American system with audiologists on the academic plane when I mention that even our system

functions satisfactorily and at an extremely reasonable cost I fully agree what Professor Jongkees stressed This holds true also when measuring

The next link in the chain is the measuring apparatus which must be of only one type—namely the best But which is the best today? The market is flooded with a wide variety of makes some of them old faithfuls that have been around for a good decade and are still going strong Then there are a number of new designs some of them good and expensive others just expensive They all have one thing in common however an elegant control panel with plenty of scales and *knobs which find their greatest value in the polychrome brochures* An audiometer for routine use does not have to be a full orchestra a trio can be enough even for an extremely enjoyable performance The more voices there are the greater the chance of an error Too many cooks spoil the broth I think you say Then on delivery the audiometer must fulfil the requirements stipulated at the meeting of the International Electric Commission at Baden Baden in 1962 The norms have been accepted by for instance the United States and England but there is also a tougher line and a serious demand for a precision tone audiometer This line has been advanced by the Scandinavian countries and aims to displace the other norms Remember the norms must apply not only to the *type* but to the particular instrument delivered to the otologist Then it is no less important that the audiometer shall not change its electro acoustic properties after a period of use A regular calibration check is therefore essential To return again to the state of affairs in Sweden for the last 20 years more than 90 per cent of the audiometers used have been the Amplivox these are taken back by the supplier every year for a check up The system functioned excellently until recently when in a few of the municipal hospitals short sighted financial interest prevailed over quality and common sense

From sounds to things the most sensitive component of the audiometer is the bone conduction receiver The earphones are certainly important in themselves but not as a source of error They are robust and easily regulated and calibrated in short they almost never give trouble The bone conduction receiver however is more of a sensitive precision instrument the calibration of which is easily upset It is difficult to discover and difficult to put right even for a well equipped servicing work shop But although the bone conduction receiver is precise it gives audiograms that in Menière s disease above all do not provide a correct picture of the function or more correctly the malfunction of the hearing organ This is what happens according to Groen et us and others

A pure tone from an audiometer is never absolutely pure but apart from the fundamental (f) always contains some harmonics the second or third (k_2 and k_3) of which is usually the strongest

This distortion may arise either in the tone generator or amplifier stage of the audiometer or in the earphones or bone conduction receiver The harmonic distortion is expressed as a percentage

For the sake of simplicity I shall consider the second harmonic either alone

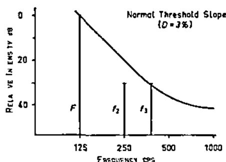


Fig 1

or with the third In reality these may appear together and with even higher ones up to the fifth harmonic has been detected in some audiometers (no names) The percentage distortion in this example denotes the amplitude of the respective harmonics in relation to the fundamental A distortion of say, 5 per cent thus implies that the amplitude of the disturbing harmonics is 25 db below that of the fundamental In the present norms for audiometers a difference of 30 db between the fundamental and the harmonics is permitted according to the British Standard and according to the ASA not more than 25 db In the following example a difference of 30 db has been chosen that is to say the best or the strictest standard

It is then found that even in the earphones at a hearing loss of 30 db and a test frequency of 125 cps the third overtone (k 3) is heard about 12 db above the threshold value for the tested tone The distortion for the bone conduction receiver is considerably higher than for the earphones but there are no standards since it is practically impossible to determine the distortion For a bone conduction receiver of superior quality it will be at least 10 per cent In the example (Fig 3) the second and third harmonics will lie 6 and 20 db respectively above the threshold when measuring a hearing loss of 20 db (250 cps) Since the audiometer is set at 250 cps and the patient perceives a tone

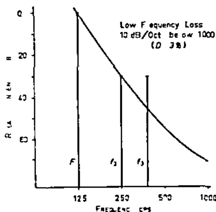


Fig 2

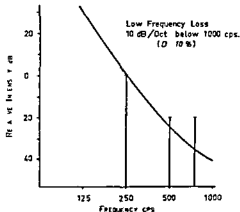


Fig 3

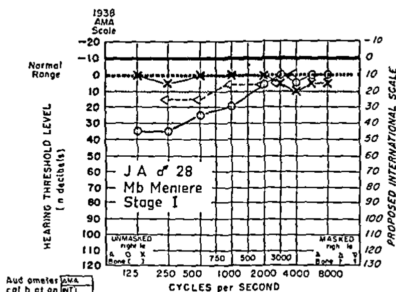


Fig 4

the bone conduction values will be too good and the diastasis between the air and the bone curves will give the typical picture of conductive loss (Fig 4)

From the standpoint of hearing loss Meniere s disease may be divided into an initial and a static stage The former is characterized by objectively distinct fluctuations in hearing ability At the same time there are a corresponding pressure sensation and tinnitus After a widely varying period the hearing loss may increase and enter the static stage which appears to be irreversible The tinnitus will then usually be permanent while the pressure sensation may disappear

The variability in hearing acuity in the initial stage differs widely from one case to another but when the hearing loss can be recorded the tone audiogram is typical It shows a low frequency loss of the neurogenic type (Fig 4) This term is a convenient one since it is still uncertain whether it is a question of a manifest nerve injury It is conceivable that there is a hydrodynamically complicated stimulation of the basilar membrane as a result of an endolymphatic hydrops This possibility would account for both the remarkable spontaneous remissions and the typical audiogram which contrasts strikingly with the sharp fall in the ordinary perceptive hearing loss towards the higher frequencies

Whatever may be the type of functional disturbance the reduction in low frequencies is definitely cochlear for there is marked and usually complete recruitment In this connection we may do well to recall Fowler s definition Recruitment is a pathologically rapid growth of auditory sensation as a function of the increase in intensity In Fowler s subjective binaural balance test there is a complete compensation that is to say the strong tones in the defective frequency range where there is a hearing loss give the same auditory sensation as in the normal ear If the objective recruitment test is used in

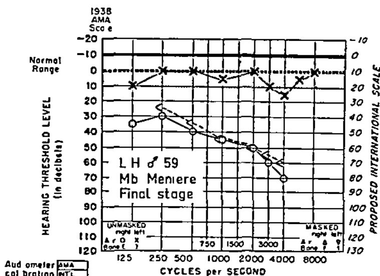


Fig 5

which the acoustic stapedial reflex is elicited, the reflex thresholds of both ears are found to be at the same level The Békésy audiogram on the other hand, had the advantage of reproducing from the frequency standpoint, a continuous picture of the hearing loss As a rule, however, it does not show the reduction in difference limen which was earlier interpreted as a sign of recruitment This negative result of the Békésy audiogram is one reason why, as Klockhoff maintains, the Békésy audiometry is not to be regarded so much as a recruitment test but as a means of detecting hair cell damage

As might be expected from the picture provided by tone audiometry, during the fluctuating stage the patient does not suffer from any practical difficulty in hearing For one thing the affection is usually unilateral, and for another a low frequency reduction does not involve any particular hearing loss Through the intact upper frequency range the patient can hear quite adequately not only conversation but also whispering Here lies a real pitfall The patient has a pressure sensation, the doctor checks the whispering distance and finding it more or less satisfactory, neglects to make a tone audiogram and has the impression of a slight conductive loss Now, any kind of tubar therapy is introduced, the hearing enters an improving phase of the Menière s cycle and the otologist s file of false diagnoses is increased by one

The initial fluctuating stage of the hearing loss may last from weeks to years If some type of conservative therapy is intended (in a case of Menière's disease) it should almost certainly be done at this stage There are presumably cases that spontaneously recover, but usually the hearing loss develops towards the serious irreversible stage, the symptoms becoming permanent as the fluctuations cease The tone audiogram now often shows a flat loss, Fig 5 which may be located at different levels but usually implies a notice-

able hearing defect of the affected ear There is still recruitment often complete and the Békésy audiogram displays a decreased difference limen especially in the higher frequency range as a sign of hair cell damage In agreement with the tone audiogram both whispering and conversation distance are of course reduced Speech audiometry tests reveal varying grades of discrimination loss which may be so marked that even with a hearing aid the ear is useless from the information standpoint The patient however sometimes has the impression that he receives more information by the way of this ear than he actually does for the recruitment phenomenon gives rise to substantial sensations of sound volume in the affected ear which the patient likes—or dislikes but the information is obtained via the other usually healthy side In the cases in which destruction of the labyrinth with consequent hearing loss is intended it is therefore important from the psychological aspect that the patient should be shown by tests just how useless the affected ear really is

Where there is hearing loss of the perceptive type tinnitus and disturbed balance frequently a pressure sensation and migraine type headache it is necessary to perform a differential diagnosis versus a retrocochlear process In the initial stage it should be possible to exclude tumour of the acoustic nerve by virtue of the typical marked fluctuation in the hearing loss In the final static stage it should be ensured that there is a degree of recruitment that is acceptable in relation to the hearing loss The possibility of a tumour plus low grade recruitment from some other cause must be excluded this can be done most simply by Fowler s subjective balance test or better still by eliciting the objective acoustic stapedius reflex

ORIGIN OF THE NYSTAGMUS ARISING DURING AND AFTER ULTRA-SONIC DESTRUCTIVE IRRADIATION OF THE VESTIBULAR APPARATUS

MICHELE ARSLAN
Padua, Italy

PREMISES

The phenomena occurring after ultrasonic irradiation of the vestibular apparatus by the severe form of Meniere's disease (to which Sjoberg and co-workers have dedicated an excellent monography) have led to the discussion of interesting problems of labyrinthine physiology. The object of our experimental research on rabbits, carried out with the collaboration of O. Sala & G. Molinari (1960 and 1962), wants to establish the cause of the following facts.

1. Is the nystagmus (of the "irritative" type) which appears in the beginning and during ultrasonic irradiation due to the histofunctional modifications induced into the ampullar receptors by the ultrasonic beam, or is it due only to the endolymphatic currents which are generated by the heating effect which always accompanies the ultrasonic irradiation (i.e. by a thermal stimulus, with the same mechanism which lies at the basis of provoked nystagmus)?

2. By varying the position of the head during the appearance of the irritative nystagmus during the ultrasonic irradiation, are there any variations and modifications of nystagmus?

3. The "paralytic" nystagmus which appears at the end of the irradiation and/or after it, is it due to a specific destructive ultrasonic effect upon the neuroepithelium? In this respect account must be taken of the histological findings of destructive lesions of the ampullar neuro-sensorial epithelium which De Stefani has demonstrated by experiments on animals in 1954 and successively confirmed by several authors (Aragno 1960, Brain *et al.* 1960, Lischietto 1960, McLay *et al.* 1961, Sjoberg and co-workers 1963).

Angell James and co-workers studied the physical events of ultrasonic irradiation at the temporal bone, determining the way of penetration of the ultrasonic beam into the bone, the heating effect upon the irradiation surface and in the temporal bone, even when, during the irradiation, the mastoid cavity was undergoing a continuous irrigation (50 cc per min) of 39°C water etc. The results they obtained are very important.

MATERIAL AND METHODS

By following some suitable procedures, which have been described by Botner & Sala (1960), it appears very easy to apply in animals the direct

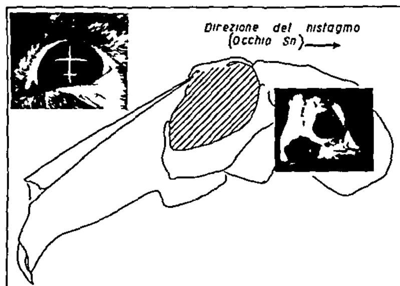


FIG 1 —Experimental ultrasonic irradiation on rabbit by different head positions (Direzione del nistagmo = nystagmus direction (Occhio sn) = (Left eye)
Head position *a* Arrow indicates the direct on of the endolymphatic current and of the slow phase of consequent nystagmus The variable length of *the arrow corresponds to the* variable intensity of the endolymphatic current × indicates the most lateral (external) position of the lateral semicircular canal where the heating effect is the highest Cross on the eye according to Magnus technique

ultrasonic irradiation of the left posterior labyrinth This procedure was carried out on rabbits by placing the applicator rod into direct contact with the mastoid surface in fact the periotic bone of the rabbit is particularly compact and has no interpositions of any pneumatic bone containing air cells and for this reason by ultrasonic irradiation it is possible to obtain a clear nystagmus as the lateral semicircular canal runs remarkably close to the external mastoid cortex

During the whole experimental work the intensity of ultrasonic irradiation was always kept at a value of 13 W/cm² measured by the Federici dosimeter (us 0 8 W)

The transducer was constantly in syntony checked by means of an appropriate device

I

While the head of the animal is in its customary posture (position *a*) there appears an irritative nystagmus during ultrasonic irradiation with jerks (along the transversal plane of the orbit) which when the *left* labyrinth is being irradiated is directed caudal in the left eye and directed rostral in the right eye (Fig 1)

While the irradiation was continued the animal was slowly rotated so as to make it reach different positions in space the well known compensatory modifications of the eyeballs appeared (otolithic reflexes)

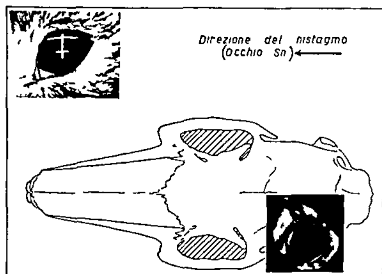


Fig 2.—Head Position *b*

In position (*b*) reached during irradiation by a slow 90° rotation of the animal to the left we observed constantly after a few seconds that a reversal of the nystagmus appeared in position (*a*) in fact, nystagmus jerks though still moving along the transversal plane of the orbit became directed rostrally in the left eye and directed caudally in the right one (Fig 2) In position (c) obtained by a slow 90° rotation of the head (and body) to the right nystagmus—which moves along the transversal plane of the orbit in this case also—grows less frequent and has a smaller amplitude When some small movements in this position are impressed on the animal's head nystagmus jerks reveal the same amplitude and speed both in the slow and

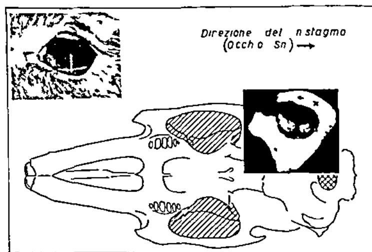


Fig 3.—Head Position *c*

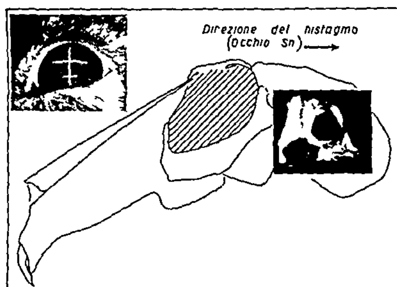


FIG. 1.—Experimental ultrasonic irradiation on rabbit by different head positions (Direzione del nistagmo = nystagmus direction (Occhio sn.) = (Left eye).
Head position *a*. Arrow indicates the direction of the endolymphatic current and of the slow phase of consequent nystagmus. The variable length of the arrow corresponds to the variable intensity of the endolymphatic current. × indicates the most lateral (external) position of the lateral semicircular canal where the heating effect is the highest. Cross on the eye according to Magnus technique.

ultrasonic irradiation of the left posterior labyrinth. This procedure was carried out on rabbits by placing the applicator rod into direct contact with the mastoid surface: in fact the periotic bone of the rabbit is particularly compact and has no interpositions of any pneumatic bone containing air cells and for this reason by ultrasonic irradiation it is possible to obtain a clear nystagmus as the lateral semicircular canal runs remarkably close to the external mastoid cortex.

During the whole experimental work the intensity of ultrasonic irradiation was always kept at a value of 1.3 W/cm² measured by the Federici dosimeter (… us 0.8 W).

The transducer was constantly in syntony checked by means of an appropriate device.

I

While the head of the animal is in its customary posture (position *a*), there appears an irritative nystagmus during ultrasonic *irradiation* with jerks (along the transversal plane of the orbit) which, when the *left* labyrinth is being irradiated, is directed caudal in the left eye and directed rostral in the right eye (Fig. 1).

While the irradiation was continued the animal was slowly rotated so as to make it reach different positions in space: the well known compensatory modifications of the eyeballs appear [illegible] reflexes).

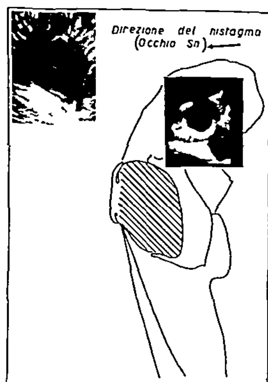


Fig 5 —Head Position e

diation was finished, and irradiator taken away from the mastoid in every experiment a paralytic' nystagmus appeared which lasted for hours and hours

Comments When during ultrasonic irradiation a nystagmus appears it does not seem to be related to a direct stimulation of the sensorial neuro

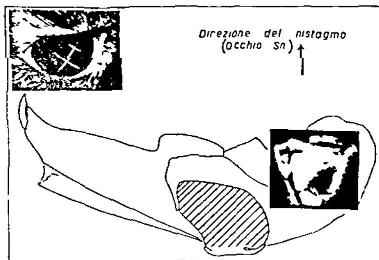


Fig 6 —Head Position f

epithelium in fact by changing the position of the head in space it is possible to invert its direction though the direction of the ultrasonic beam in relation to the mastoid's surface is kept unmodified. Hence this irritative nystagmus is no doubt provoked by the heating effect which accompanies the ultrasonic irradiation, i.e. by the endolymph currents which are the effect of the heat induction in the lateral semicircular canal.

When it happens that the ampulla of the lateral semicircular canal (s.c.) has a higher level than the outermost tract of the same canal (where the heating effect is greater) the endolymph current directed towards the utricle is of an intensity which increases the more the lateral s.c. approaches the vertical (positions (*c*), (*a*) and (*d*) respectively). On the other hand it is well known that the intensity of the eye nystagmus (in our case along the transversal plane of the orbit) is proportional to the intensity of the endolymph currents which originate in the semicircular canals.

On the contrary, the endolymph current has an utriculofugal direction when the cupola is below the outermost tract of the lateral s.c. where, as we mentioned above, the heating effect is greater. Hence in this case, the direction of the eye nystagmus is reversed though still remaining in the transversal plane of the orbit. Here too the intensity of nystagmus is proportional to the intensity of the endolymph current which for the above mentioned reasons is more evident in position (*e*) than in position (*b*).

By supine position (*f*) with the body of the rabbit on the horizontal plane and its head bent 30° forward the lateral s.c. is practically on a horizontal plane, that is not in a favourable position (indifferent position) for the creation of endolymph currents but vertical semicircular canals are in the most favourable position and therefore during ultrasonic irradiation there arise endolymph currents which provoke a nystagmus which moves along the vertical plane.

These results which depend on the thermic side effect of the ultrasonic irradiation are perfectly in accord with the clinical observation of *change-ment of the nystagmus direction (when it is, as usually, provoked with the* classical clinical test) when after water irrigation the head changes its position (position I, II, III etc. after Brunnings, indifferent or optimum position etc.). Furthermore we carried out control experiments in the rabbit by means of prolonged cold water irrigation (15–20 min and more) at a temperature of 10°C: in this case the *identical* modifications of the position of the head in space (positions *a*, *b*, *c*, *d*, *e*, *f*) are followed by the same nystagmus modifications which are absolutely equal (but in the opposite direction) to those obtained with ultrasound (heat stimulation).

Concerning the question whether during ultrasonic irradiation given by our technique we can prove a modified activity of the otolith, the results show that ultrasonic irradiation when applied on the lateral s.c., cannot modify the compensatory ocular positions caused by the otoliths.

Besides, the results of these experiences explain a very singular event that sometimes is to be seen during ultrasonic irradiation performed in patients

suffering from a severe form of Meniere s disease In a few cases we noticed that just after applying the irradiator to the bone labyrinth a paralytic nystagmus appears instead of the usual irritative one This paralytic nystagmus lasts throughout the irradiation time (25–30 minutes) This singular fact has taken place especially since the application of the new technique was started by which instead on the lateral semicircular canal convexity the irradiator was set on the area posterior to it namely at the level of the vestibule (between the two canals the lateral and the posterior one) (Arslan 1962)

The inversion of the direction of the nystagmus appearing during irradiation results from the fact that the thermic effect can occasionally provoke an endolymphatic current from the vestibule *to* the lateral canal bending the cupola off the utriculus and not towards it as happens by the old technique i e of irradiation on the canal convexity

The presence of a nystagmus of a paralytic rather than irritative type *during* irradiation may induce operators to suppose it difficult to spot the paralytic nystagmus appearing during and after irradiation But the two nystagmus are clearly distinct the one during irradiation is more frequent always mixed (horizontal rotatory) and has some particular characteristics which the operator will quickly learn with experience

II

By other experiments we arranged a source of heat by which it was possible to obtain the same thermic curve measured at the tip of the treatment head applied for the ultrasonic irradiation Thus we had a copper rod of the same dimensions as the ultrasonic applicator rod and provided at the tip with an electric resistance the temperature of which was adjusted by a thermistor

Once the copper rod had reached a temperature of 50°C or even more it was applied directly to the same left semicircular canal—following the method we mentioned above

As soon as the copper rod was applied to the temporal bone there appeared an irritative nystagmus in the transversal plane of the orbit which disappeared after about 10 min the eye nystagmus appeared again—though always for a short time (2–3 min)—both when the animal was set in position (*d*) (animal vertical with its head up) and when the copper rod was applied again to the temporal bone after suspension of the caloric irradiation for a few minutes

We never observed in this condition the appearance of a paralytic nystagmus either at the end of the application of the copper rod or during the above mentioned intervals (between one period of heating and the following one) even when the thermic application had gone on uninterruptedly for a period of two hours

To obtain a paralytic nystagmus i e the syndrome of unilateral

labyrinthine destruction we had to raise the temperature of the copper rod considerably (over 110°–120°C) and to apply the rod uninterruptedly for a period of time which we observed had to be no shorter than two hours

III

With another experiment series ultrasonic irradiation was carried out in the manner described above (left labyrinth intensity of 13 W/cm² (u s = 0 8 W) irradiation time 40 50 min) the ultrasonic applicator rod however, was constantly maintained at a temperature of strictly 38°C by means of a cooling system consisting of a thin copper pipe coiled around the applicator rod in which water circulated at variable temperature and speed In this case also the temperature of the applicator rod was checked by a thermistor as described above This cooling system is similar to that which was for the first time proposed by Angell James and co workers

By this research we proved that a cold ultrasonic irradiation is not followed during irradiation by any nystagmus even though the animal s position in space was changed (positions *a b c, d e f*) A few groups of slight jerks appeared only when some very slight (< 0 5°C) and transitory temperature variations at the tip of the applicator rod occurred

After this irradiation no paralytic nystagmus appeared either but if the animals were prodded so as to make rapid movements they walked un steadily and there appeared groups of twitches of a sometimes paralytic and sometimes irritative nystagmus This condition of latent lack of balance in creased after 36 72 hours and then disappeared slowly Acceleratory stimula tion—made 20 30 days later—proved the presence of hyporeflexia of the irradiate labyrinth (Molinari 1960)

A group of six animals was therefore subjected to a continuous cold ultrasonic irradiation for 2 hours always at the same intensity (13 W/ cm² 0 8 W) At the end of the irradiation we observed the appearance of an irritative nystagmus which continued for several hours and *was not reversed when the position of the animal s head in space was modified ac cording to the usual method described above* (positions *a b c d e f*) We could thus exclude the possibility that nystagmus obtained in this way was caused by endolymph currents provoked by heating effect of any kind what ever

This irritative nystagmus grew fainter and after 8 12 hours a paralytic nystagmus appeared attended by the well known unilateral labyrinthine destruction syndrome which though growing fainter, persisted during the days that followed of course this paralytic nystagmus was not reversed either when the position of the head in space was changed

RESULTS

The answers to the questions proposed in the premises of this paper are the following

Ad I The irritative nystagmus which appears at the beginning and during

ultrasonic destructive irradiation of the vestibular apparatus depends on the heating effect developed by the applicator rod This heating effect acts as a strong thermic (heat) stimulation and induces endolymphatic currents

to 2 Varying the position of the head during the appearance of this thermic nystagmus it changes its direction and intensity (as it is known for any thermic nystagmus since a long time) and becomes more intense as the plane of the canal approaches the vertical

to 3 The pure ultrasonic energy acts directly upon the neuroepithelium this action in its *first phase* provokes a functional protoplasmatic excitation (and some biochemical modifications of the endolymph too) which is revealed by an irritative nystagmus much less intense than the thermic one

Then the heating side effect generated by the applicator rod precedes the pure ultrasonic action and modifying the state of molecular aggregation of the endolymph *aids the diffusion of the ultrasonic beam and facilitates its vehiclement to the neuroepithelium* (Muzzioli) Angell James s experiences on the reflection of the ultrasonic waves in the walls of the semicircular canal bear out this hypothesis

The thermic nystagmus which originates during ultrasonic irradiation shows a jerk amplitude and an intensity which progressively decreases owing to the progressive formation in the neuroepithelium of protoplasmatic lesions which are the effects of the specific lesioning action (*second phase*) of ultrasound at the level of the neurosensorial epithelium (temperature rise agitation caviation etc) at a certain moment the lesions of this epithelium grow so extensive that they induce a functional paralysis of the vestibular receptor which manifests itself by the appearance of paralytic nystagmus

The selective destruction of the neuroepithelia of the cristae ampullaris is due to two factors (1) the neuroepithelium is the more differentiated tissue of the inner ear and consequently it is the more exposed one to the destructive effect of ultrasound (2) the dirigibility of the ultrasonic beam that is the property of propagating only in the direction in which it is emitted This destruction proved by the histological researches (De Stefani 1954 and others) arises only when ultrasonic irradiation is continued for a certain period of time and is connected with the intensity of the ultrasonic beam its wavelength and other factors The appearance of a paralytic nystagmus at the end of irradiation is the funct onal manifestation of this destruction it causes a functional def cit both because of the number of neur sensorial cells affected and because of the severity of the endocellular lesi ns We pointed out that the destruction is never cc mpleted at once and is progressive in fact after the irradiation there still exists within 2 3 months a certain vestibular reflectivity which later in nearly all cases is replaced by a late areflexia (Arslan 1953)

If the ultrasonic neuroepithelial destruction is less intense (because of its lower intensity or because it is applied for a shorter time or because it is taken off the thermic side effect) there is only partial lesion of the receptor at

the end of the irradiation in this case an irritative nystagmus appears at a later time which is not reversed by causing changes in the position of the head in space The endocellular light modifications the formal aspect of which is still unknown cause an irritative condition in the neurosensorial epithelium but later as a progressive atrophy will arise during the days following ultrasonic irradiation there appears a paralytic nystagmus which however is never accompanied by a clear unilateral labyrinthine destruction syndrome

CLINICAL CONSIDERATIONS

We believe that many of the phenomena observed in man during direct ultrasonic irradiation of the posterior labyrinth following our ultrasonic method (e g the inversion of the ocular nystagmus appearing during the ultrasonic irradiation when the position of the head is changed (Bötner 1960) the irritative nystagmus which may continue for several hours also when the ultrasonic irradiation has been stopped etc) can be explained by the experimental work here related

According to Angell James and co workers Sjöberg Kossoff etc we must try to perform always the ultrasonic irradiation using a generator by which the thermic side effect has only the intensity sufficient to provoke an irritative nystagmus which must be the guide of the ultrasonic waves In this way ultrasound is vehicled to the vestibule and to the crista

In order to follow the best technique the following requirements must be fulfilled

1 *High efficiency of ultrasonic energy* The quantity of electric energy from the oscillating circuit that is turned into ultrasonic energy at the transductor level must be as high as possible

The electric energy that is not turned into ultrasonic energy becomes thermic energy (thermic side effect)

2 *Thermic side effect* This thermic side effect is the origin of the irritative nystagmus to be observed during ultrasonic irradiation Now the continuous presence of this nystagmus as we repeatedly stressed is indispensable to successful surgery in Menière s disease as it shows the exact course of the ultrasonic irradiation of the posterior labyrinth

Therefore according to the researches of Angell James and co workers and to our researches a well devised ultrasonic irradiator must deliver a temperature to be checked at the rod tip over 40°C but not beyond 47°C

3 *Ultrasonic intensity* The ultrasonic power should be sufficient to destroy the vestibular receptors in a short time *without causing injuries to the underlying organs* Very rewarding results may be achieved by employing intensity around 1 w s watt for a period of 25 30 minutes

4 *Directivity of the ultrasonic beam* This property allows to direct the ultrasonic beam exactly in the direction desired without a great lateral leakage

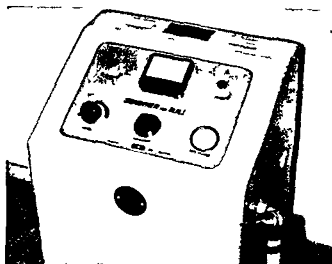


Fig 7 The 2nd model of the Federici generator frequency 3 MHz intensity 1 u s watt, without cooling system

5 *Frequency and penetrability of the ultrasonic waves* As the dirigibility increases with ultrasonic frequency, it is recommendable to use frequencies superior to 1 megahertz The latest generators (Angell James, Kossoff, Frederici 2nd model) have a 3 MHz frequency (Figs 7 and 8)

However, since the ultrasonic beam reaches the vestibular receptors

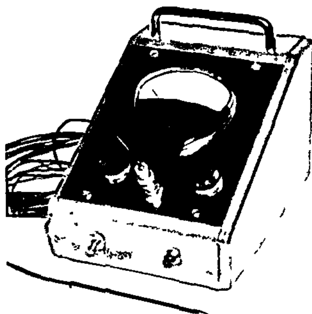


Fig 8 The Kossoff ultrasonic generator frequency 3 MHz intensity 1 u s watt without cooling system The applicator rod can be used for Menière's disease for hypophysectomy etc

through a bone layer and is only partly absorbed by the latter, and since penetrability decreases with the increasing of the frequency, it is advisable not to use frequencies over 3 MHz In fact, beams of higher frequency would be totally absorbed by the bone lying between the ultrasonic rod and the vestibular receptors

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THE PHYSICAL AND BIOLOGICAL PROPERTIES OF ULTRASOUND AND CLINICAL EXPERIENCE

J Angell James, H F Freundlich, M A Bullen, P N T Wells, and D P C Williams
Bristol, England

Physical Effects

Ultrasonics are vibrating waves of frequencies above 20,000 cycles and ranging up to 500 megacycles The properties of these waves gradually change as the frequency rises until at the high frequencies they begin to resemble light rather than sound For this reason frequency bands having different properties are used for different purposes They all need a medium for propagation It is the minute size of the wave that endows it with its unique properties The most important effects of these waves are as follows

1 Simple agitation which may reach great intensity causing rupture of materials
2 Cavitation
3 Temperature rise
4 Alteration of PH due to release of radicles
5 Chemical changes such as oxidation and degeneration of large molecules, particularly of proteins
6 Increased permeability of membranes at low intensities and rupture at high intensities
7 Increased biochemical activities of enzymes in cells at low intensities and destruction at high
8 Streaming

Selection of Frequency for Specific Purposes

40 kc (kilocycle) 300 kc for echo signalling under water
Below 100 kc for cleaning largely by cavitation and agitation
400 kc for emulsification
500 kc for testing large grain materials
1000 kc (1 mega) for biological and ordinary grain material testing
5000 kc (5 mega) for very fine homogeneous testing

For biological effects it would appear that the most important frequency range lies between 750 kc and 5 megacycles In this range and at relatively low intensities all the above effects can be induced except cavitation This occurs only in liquids when microscopic bubbles of gas or vapour develop at the wave nodes when the absolute pressure at this point is less than the vapour pressure of the fluid

Our interest in ultrasonics as a surgical tool was aroused by Arslan's introduction of the ultrasonic destruction of the labyrinth in Menière's disease (1953). We have worked at three different frequencies—approximately 1 megacycle, 3 megacycles and 5 megacycles. We began our work with the Arslan-Federici equipment employing a crystal transducer and metal cone focussing at approximately 900 kc. By measurement we showed that this generated great heat from absorption of the ultrasonics at two sites. The first was in the metal rod where there was much interference and absorption and the second was in the temporal bone itself where the ultrasonics were poorly conducted and quickly absorbed. The efficiency of the apparatus was only 2%, the remaining 98% of energy being transformed into heat. The temperature at the tip of the rod rose to no less than 90°C if it was not adequately cooled. In the bone the half intensity power distance at 1 megacycle proved to be ¾ mm. This is in sharp contrast to the half intensity power distance in water which is 15 metres. It was thus apparent that in the Arslan technique of ultrasonic destruction of the labyrinth without cooling, heat must play a considerable part in addition to the pure effect of the ultrasonics. In view of the poor conductivity of bone the idea of altering the aiming of the focussed ultrasonic beam to pick out different parts of the labyrinth hardly seemed to be feasible.

We therefore concentrated on applying the maximum ultrasonic power into the labyrinth fluids relying on the extremely efficient conduction these provided and the wave guide of the bony walls of the canal and vestibule to carry the ultrasonics to the sensory neuroepithelium which it was the intention to destroy. Since the cavity and the fluids filling the cochlea are continuous with those of the vestibular apparatus it seemed extraordinary that the cochlea should not also be effected. We have no doubt that it is effected but much less severely than the vestibular apparatus. It is probable that this is due to the angle of entrance of the cochlea duct into the vestibule which baffles to a considerable degree the transmission of the waves as they are reflected repeatedly back and forth from the bony vestibular walls.

Originally used as a destructive weapon, it was a surprise to realise after clinical application that in some patients suffering from Menière's disease there was an actual improvement in hearing and reduction in tinnitus together with a loss of the sensation of blocking or fullness of the ear. We doubt if this can be accounted for by the natural variations in the disease alone. To which of the biological actions of the ultrasound can this be attributed? Two possibilities present themselves. It may be due to increasing the permeability of the endolymphatic system reducing the distension and restoring blood circulation or there may be some action on the cells of the stria vascularis altering endolymph secretion and the maintenance of the electrolyte balance and gradients.

Until recently we have concentrated on trying to discover the most suitable frequency and develop a reliable ultrasonic generator and a satisfactory technique of application for the purpose of destruction of the vestibular

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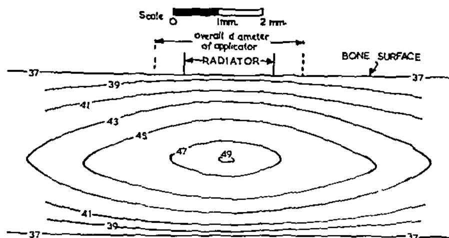


Fig. 1. Isotherms in temporal bone. Transducer and water filled velocity transformer with radiating area 0.037 cm² operating at 20 W/cm². Water flow rate 22 cm³/min. Temperatures in °C.

In assessing these results allowance must be made for the fact that

1. the ordinary course of Menière's disease is notoriously unpredictable and its severity often waxes and wanes
2. The results will not be confirmed until several years have elapsed
3. We have only accepted patients for operation when full medical treatment has failed and the symptoms were severe and many of the patients in this series were very difficult problem cases referred to us by other consultants

The only complication encountered in this series was facial paralysis. This occurred once in the 1 megacycle group due to mechanical failure in the flow of coolant. It occurred four times in the contact group due to coolant failure and spot heating. The two delayed pareses at the sixth day in this group are specially interesting as on the same day a sudden severe drop in hearing perception was noted indicating some pathological reaction throughout the inner ear as well as in the facial nerve. Perhaps this is related to delayed facial paralysis observed at the sixth or seventh day after head injury. All the cases of facial paralysis have recovered but a decompression was performed on one of the contact transducer cases. The others lasted only a few days or weeks. No case has occurred since the ultrasonic power has been reduced to a maximum of 22 watts/cm². Temporal bone heating at this power is shown in the isotherm diagram. If the transducer is carefully placed over the clearly exposed wide blue line of the lateral canal and aimed forward in the line of the semi circular canal avoiding the fallopian canal and kept in contact with the bone the facial nerve should not receive any direct irradiation. It is, however, still at risk from heating if the flow of coolant fails or the power is turned up above 22 watts/cm².

Although ultrasonics can be a dangerous weapon if not very well under

stood and controlled, they have provided a means of giving immense relief to many patients who needed destruction of the diseased labyrinth but wished to retain some hearing and have some relief from tinnitus. Much more experience is needed, however, in assessing the optimum dose.

It should be possible with research and clinical experience to assess the doses needed much more accurately so that certain elimination of the vertigo is achieved but the optimum benefit follows from the effect of the ultrasonics on the endolymph secretion, pressure and electrolyte balance and microcirculation.

ACKNOWLEDGMENTS

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CLINICAL EXPERIENCE FROM THE TREATMENT OF MENIERE'S DISEASE

ARNE SJÖBERG
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It has been rightly said that *one gropes in the dark when seeking* of therapy for Meniere's disease. The pathogenesis of the disease is st clear and it seems logical that the conservative treatment therefore *multi-facetted and intricate*.

For want of space I cannot go too much into detail. I have therefore pared a schematic presentation (Scheme I), which will demonstrate th blem quickly and simply. The first heading is *Psychotherapy*.

I have tried to emphasize that psychotherapy in conjunction with resting, good sleep, perhaps sedatives and abstaining from smoki essential. We must always be aware that we are often dealing with psyc labile stressed persons who must be brought to a state of psychical relax Their uneasiness and anxiety when facing the psychical shock whic recurring attacks bring forth must be moderated. Much patience and passion is required of the attending physician before the continued treat of the affection can be discussed quietly. The patient must learn to acce troublesome affliction and he must be brought under psychosomatic co

It is the rule in *medicating* therapy to administer drugs of two type those which work symptomatically on the acute attack of vertigo wi nausea and vestibular in coordination, and (2) medicines which will the patient to a symptom free interval.

We acknowledge that the inspiration to this medicating treatment is d the experiences from both experimental studies and the treatment of *m sickness* before, during and after the last world war.

The various groups of medicaments which come into use are not st different from each other but are naturally chosen with reference t varying hypothetical etiological interpretations. In our diagram (Schem we see many different drugs pass in review—anything from sedatives central hypnotic effect to vestibular depressant cholinergic remedies fo sickness of the antihistamine type with antiallergic effect.

There are also vasodilating substances which may have an antier effect. In this group can possibly be included the effect of procaine xyl aine administered intravenously (R. Barany — Tinnitus—intravenou cal anesthetic 1935, *Hilger* 1949, *Fowler* 1953, *Gejrot* 1963).

After lectures given (1) May 30th 1963 at the International Vestibular Symposium s la Sweden (2) June 1 th 1963 in Oslo Norway at the *opening of the XVth Congress* Scandinavian Oto-Laryngological Society

Scheme I. MEDICAL TREATMENT OF MENIÈRE'S DISEASE

I. PSYCHOTHERAPY

II. MEDICATING THERAPY (DRUGS)

1. With central sedative hypnotic effect. (Barbiturates, antihistamines, ataractics.)
2. With damping effect on the excitability of the vestibular apparatus. (Antihistamines and other drugs against motion sickness with atropine-, anticholinergic and antiallergic effects. Intravenous injections: procaine, xylocaine.)
3. With antiangiospastic and vasodilatory action, e.g. nicotinic acid preparations, theophylline, dihydroergotoxin (Hydergin). Stellate ganglion blocking.
4. With polypotent effect—psychosedative, arteriole dilating action, weak vestibular damping and anticholinergic effect. (Chlorpromazine.)
5. Glycocorticoids with inhibition of inflammation and antiallergic effect. (Influence on midbrain pituitary gland.)
6. Desensitization with histamine.
7. Vitamins A, E with protective action on epithelia. C-P against capillary fragility.

III. VASCULAR AND CAPILLARY DYSFUNCTION WITH INTRACELLULAR OEDEMA (Mygind-Dederding)
Correction of the fluid and electrolyte balance. Salt-poor diet. Limitation of fluid and calorie intake etc.

IV. HYDROPS OF THE ENDOLABYRINTH. (A) OVERPRODUCTION, (B) UNDERABSORPTION OF ENDOLYMPH, (C) DERANGEMENTS OF CAPILLARY PERMEABILITY.
Diuretics. Hydrochlorothiazide.

V. BILATERAL INTERRUPTION OF VESTIBULAR PATHWAYS BY STREPTOMYCIN

For us in the Scandinavian countries it is a pleasant task today to bring to mind that it was the two famous Danes—S. H. Mygind and Dida Dederding—who in the early 30's inaugurated the now classic fundamental conservative treatment of Menière's disease. The hypothesis taken by these two researchers was that the shock-like sudden attack of vertigo was not to be regarded as a disease *sui generis*, but rather as a definite individual reaction pattern in a *predisposed labyrinth*. *Through some form of* vascular and capillary dysfunction, an intracellular oedema—a fluid retention—will occur.

According to Mygind and Dederding the disturbed fluid and the electrolyte balance must be restored together with a general fluid reduction. Salt-poor diet and diuretics, baths, massage and reduced calorie intake must also be included in the regime.

In 1926 Wittmaack set forth the concept of labyrinthine hydrops and he

SCHEME II SURGICAL TREATMENT OF MENIÈRE'S DISEASE

I CONSERVATIVE LINE WITH PRESERVATION OF INNER EAR FUNCTION—DECOMPRESSION OPERATION

(a) Drainage of the saccus endolymphaticus (G Portmann 1927) Silicon tube in the saccus as a permanent shunt into the subarachnoid space (modified acc to W House, 1962)

(b) Fenestration (Lindsay, 1946 Y Meurman 1951)

(c) Fenestration with tamponade of the semicircular canal and tympanosympathectomy (Frenckner, 1952)

II RADICAL SURGICAL LINE WITH SACRIFICE OF INNER EAR FUNCTION—LABYRINTHECTOMY

(a) Trans mastoidal extraction of the membranous semicircular canal (Cawthorne, 1938)

(b) Trans tympanal extraction of the membranous labyrinth (Schuknecht 1956 Cawthorne 1957)

III SELECTIVE INTRACRANIAL SECTION OF THE VESTIBULAR NERVE (Dandy, 1928 1933 Olivecrona 1943)

IV ULTRASONIC IRRADIATION WITH SELECTIVE VESTIBULAR DESTRUCTION AND CONSERVATION OF HEARING (Krejci 1952 Arslan 1953)

showed histological concrement in the aqueduct of the cochlea In 1938 Hallpike and Cairns were able to demonstrate histologically an enormous dilatation of the endolymphatic sac with pronounced degeneration of the sensory epithelium in Corti's organ This was later demonstrated by many other researchers latest by Harald Kristensen (on among others Dida Dederding's labyrinths) In the crests of the ampullae in the otolithmaculae and in the vestibular ganglia the degenerative changes were missing even though the caloric excitability was eliminated

As we all know the endo labyrinthine hypertension—hydrops labyrinthidis—is considered to be due to a vascular insufficiency (perhaps vasospasm)—an alteration in the capillary permeability which changes the relationship between the endolymph production and its absorption (a glaucoma of the ear or perhaps as I use to call it *Migraine labyrinthique*)

In 1946 the Finnish scientist Arno Saxén published excellent morphological investigations which are also of great importance today He presumed that the point of origin of the endolymph was the vascular stria and the secretory epithelium of the planum semilunatum at the base of the cristae *of the semi circular canals and along the side walls of the ampullae* Many researchers today are of the opinion that the endolymph is the result of a glandular secretion (Borghesan our Uppsala team and others) The final

proof of this function of the secretory epithelium has been given by Dohlman and co workers who used radio active S^{35} on pigeon labyrinths

These ideas are carried out principally in the medicating therapy of the 60 s, which continually strives to lessen a supposed labyrinthine hydrops a localized oedema through among other things the oral administration of the new mild effective diuretics of the hydrochlorothiazide type (e g Esidrex K®)

It is believed that this dehydration could also reduce the risks of a secondary sensory epithelial degeneration and bring the patient into a period of remission

If one accepts these thoughts of a disturbed fluid exchange in the inner ear —whether there is an *overproduction underabsorption or a disturbance of capillary permeability with local oedema*—then it is a simple matter to understand the other forms of suggested therapy (Scheme I) from nicotinic acid preparations glyco corticoids to vitamins

Cases with *double sided* Meniere s disease which do not respond to medicating therapy are not too uncommon (they have been estimated to be 10–30 %) For the malignant double sided cases with bilateral strongly reduced hearing one *can resort to interruption of the vestibular pathways with streptomycin*

This treatment form takes up an intermediary position to the radical surgical destructive therapy otherwise reserved for the serious invalidizing one sided cases of which none respond to internal therapy

THE SURGICAL TREATMENT (Scheme II) has developed along two main lines the conservative and the radical

I WITH THE CONSERVATIVE LINE one seeks to retain the inner ear function either completely or partly

The endolabyrinthine pressure is lessened through decompression operations

(*a*) Georges Portmann s decompression operation from 1927 with drainage of the endolymphatic sac

William House in Los Angeles has in 1962 rediscovered and modified this old decompression technique by inserting a silicone tube into the saccus as a continual endolymph drain—a shunt to the subarachnoid space

(*b*) Lindsay in 1946 and Y Meurman in 1951 have both recommended fenestration

(*c*) Frenckner in 1952 suggested fenestration with tamponing of the ampulla of the lateral semicircular canal and tympano sympathectomy

II THE RADICAL SURGICAL LINE is represented by the destructive labyrinthectomy The inner ear function is completely sacrificed In 1938 Cawthorne suggested that the membranous labyrinth should be extracted after (*a*) a *trans mastoidal approach* from a fenestration of the lateral semi circular canal But the membranous labyrinth and then in the first place the utriculus can also be destroyed (*b*) *transtympanically* by way of the oval window This

technique was presented by Schuknecht in 1956 and by Cawthorne in 1957. The results of labyrinthine destruction seem to be relatively good, mostly giving relief from dizziness and recruitment but nevertheless *resulting in a total deafness on the operated side*.

In 1960 Cawthorne claimed to have operated on more than 400 cases. But unfortunately a careful clinical follow-up of operated cases of this type has not yet been published.

III. INTRACRANIAL VESTIBULAR NERVE SECTION could principally be included in the group of conservative approaches, for also here there is an attempt to preserve the hearing. This operation was performed for the first time in 1928 by the brain surgeon Dandy and good results have been forthcoming in the Scandinavian countries from, among others, Olivecrona in 1943. This method seems to have been abandoned almost entirely for the reason that it implies too great a risk in *quoad vitam* through the craniotomy and opening of the subarachnoid space.

IV. ULTRASONIC IRRADIATION through the trans-mastoidal approach also *permits the possibility of preserving the hearing*. The primary intention here is the selective total destruction of the vestibular apparatus, but the result has in most cases been only *a partially reduced excitability*, as I will show later.

It is a fact that the choice of a surgical method for the severe invalidating cases of Meniere's disease today is between the radical surgical line with real destructive labyrinthectomy and the relatively preserving ultrasonic irradiation with a well focussed beam. The decompression method, however, also has its adherents.

Now I will describe the ultrasonic irradiation treatment of Meniere's disease in greater detail and consider this narrative to be justified as this treatment form is now timely and for the present the best treatment for those serious cases which have retained hearing and which do not respond to conservative measures.

Today the use of ultrasound in medicine is still very limited, but when searching for a new method for selective destruction of the vestibular nerve it seemed that the time had come to draw the attention to the ultrasound.

From the historical viewpoint let me remind you that it was the Vienna otologist Vyslonzil who in 1949 succeeded in experimentally irradiating and extinguishing the vestibular function in animals.

Another Vienna otologist E. Krejci took up this problem and published the results of his outstanding basic work in 1952. He had worked with Seidl at the Institute of Physics and they used a newly constructed Austrian ultrasonic apparatus. They found that the ultrasound was absorbed by the air in the mastoid process if the apparatus was placed dry against the planum mastoideum.

Krejci did his experimental work on guinea pigs and succeeded in destroying the vestibular system. By means of Preyer's ear muscle reflex, twisting movements of the auricles of the ear, and by measurement of the

cochlea potentials it was shown that the hearing was retained after "Beschallung".

To Krejci belongs indubitably the honour of having been the first one to treat a human being suffering from Ménière's disease by applying ultrasound directly against the horizontal semi-circular canal after trans-mastoidal approach and thereby execute a selective destruction of the vestibular nerve.

Because of some unhappy local circumstances Krejci was unfortunately unable to continue his work.

At the International Congress in Amsterdam in 1953 Arslan presented an Italian apparatus with which he had successfully treated his first cases of Ménière's disease.

For the past decade Arslan has been the foremost successor of Krejci and at the Congress in Paris in 1961 he reported over 600 cases treated ultrasonically, 85 % were relieved from vertigo. In 1961 Altmann and Waltner from New York showed relief from vertigo in 67 % of their cases. In 1962, as we can see here, Altmann reported 74 % relieved from vertigo—facial paralysis in 6 %. E. W. Lindahl, London Hospital, accounts for 7 cases of facial paralysis in 39 treated cases (18 %). Angell James reported 176 operated cases with relief from vertigo in 80 %.

Unfortunately it has been all too apparent that the Italian apparatus in its first form did not function with complete satisfaction. It was difficult to tune. The tip of the transducer was too large and during irradiation it became excessively hot so that it was necessary to introduce cooling by means of constant irrigation with physiological saline solution in order to avoid facial paralysis. Even necrosis of the labyrinth has been described.

To our team in Uppsala these facts became an inducement to try to design and build a new reliable apparatus which would give more power and have a smaller dimension of the tip of the transducer.

The results of our Uppsala otological research group (A. Sjöberg, J. Stahle, R. Sahl) which I will now present have been the outcome of an excellent teamwork with our physicists from the Scientific Research Council's Electronics Department, in particular *Sven Johnson*, Ph.D., who designed our new Swedish built apparatus "Ultrapoint" with a well cooled ultrasonic applicator having a narrow tip and a well concentrated sound output.

In order to understand better the principles involved here let me present a few fundamental physical principles concerning the fascinating problems of ultrasonic treatment.

It is well known that the human ear can register sound waves from 16 cps and upwards. Above 20 000–22 000 cps the oscillations become inaudible to the human ear. These high sonic frequencies, which lie above the limit of our hearing ability, are called ultrasound.

Many animals produce, as we know now, such high frequent sounds and they are also able to perceive them with their own auditory perceptors.

It has been aptly said that we human beings can experience the silence of the forest only because our upper hearing threshold is so low. Could our



Fig 1

ears but hear the ultrasound also this silence would become a deafening noise We should then for example be able to hear the cries of the bats at 45 000 cps

It is well known to everybody that sound is propagated in the form of longitudinal waves Ultrasound is transmitted to the irradiated medium—fluids and biological tissue—in the form of longitudinal pressure waves An advancing field of waves arises in the medium in which the smallest particle is subjected to alternating positive pressure forces and to negative traction forces

Actual wave peaks and troughs appear In certain materials especially the more solid ones such as bone and metals it is necessary to take into account the transverse movements of particles which result in so called shear waves torsional waves and occasionally even non penetrating surface waves

From the biological viewpoint the intensity of the ultrasound is decisive The intensity is measured in terms of watts/cm² and this measure is used for determining the proper dose For our Swedish apparatus we have instead used the power in total watts as it is measured coming out from the tip of the probe

The biological mode of action of the ultrasound is a complicated course of events Ultrasound affects the irradiated tissue in three ways

1 mechanically
2 thermally—heat producing
3 chemically

1 The *mechanical* effect is best compared to a shaking motion—a micro massage which causes the fluids to disperse and gives the impression of boiling without a significant rise in temperature

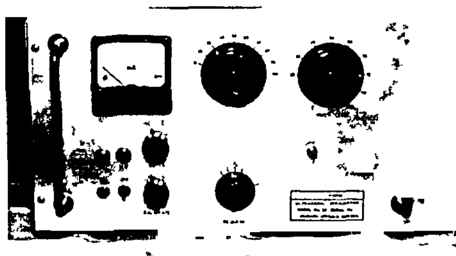


Fig. 2. The new Swedish ultrasonic apparatus "Ultrapoint".

If ultrasonic waves are reflected from a wall, standing waves are produced—a, so to speak, dramatic optical demonstration of the presence of ultrasound.

Standing waves can also arise in blood. If a little citrated blood is mixed with physiological saline solution on a microscope slide, standing waves appear when the tip of the transducer is immersed—in appearance much like the sand waves left on a beach after a storm.

This little test with the microscope slide has been of great significance to us. *We have with this test succeeded in visualizing the ultrasound both on the slide and in the wound.* Fig. 1 shows standing waves in the blood on the microscope slide. We can to a certain degree evaluate the momentary intensity of the irradiation. The test is naturally a little crude, but it is performed under the sterile conditions required during the course of the operation to check that the apparatus is working. The physicist is present during the operation, sterile scrubbed, tuning the generator and having had it calibrated beforehand.

The red and white blood corpuscles can be destroyed, resulting in a hemolysis. Ultrasound also has a sterilizing effect. Bacterial membranes and virus particles can be broken down.

2. The *thermal* effect of irradiation is due to the fact that energy is absorbed by the tissues. The heating is best compared to short wave diathermy.

3. The *chemical* effect is complicated and varied. Chemical reactions can be released or accelerated.

From the otological point of view, however, the effect of ultrasound upon bony and nervous tissue is of the greatest interest.

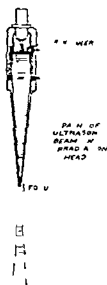


Fig 3

At least 70 % of the ultrasound which penetrates the bony tissue is converted into heat The reason for this is that the bony tissue has a very high absorption coefficient The so called half intensity distance is very short in bony tissue By half intensity distance we mean the distance which the sound penetrates into a medium before it loses half of its original intensity For bone this is approximately 1 mm while in water it is about 15 m (Angell James group 1960) In the human organism the nervous tissue is the most sensitive tissue to ultrasound Peripheral nerves have been irradiated experimentally and it has been found that the internal heating is the main cause of function loss If this heating exceeds 45°C it usually brings about a total and irreversible blocking This is vital to the otologist s point of view considering the proximity of the facial nerve to the labyrinth The sensitivity of the peripheral nerves to ultrasound and heating makes certain demands with regard to the cooling capacity of the apparatus If the tip of the transducer becomes too hot heat will also be transferred superficially to the labyrinth This heat is by itself enough to irritate the labyrinth thermally and increases the chance of facial nerve damage

The apparatus consists of two main parts (I) The *generator* which includes a radio frequency oscillator a power supply and an amplifier (Fig 2) (II) The *treatment head*—the transducer—with its cooling system (Fig 3)

Length 140 mm weight about 100 grams greatest diameter 25 mm It can be held with a pen like or pistol grip holder

The tip of the treatment head is hollow and is sealed at the front with a very thin metal membrane

The ultrasound is produced by a concave lead zirconate titanate disc For maximum clinical efficiency a power of less than 100 volts is required compared to a quartz crystal requiring several thousand volts for the same

purpose Therefore it is possible for us to use a light thin flexible cable

The treatment head is continually irrigated with distilled water which is circulated by means of a special pump

The water has a double function it conveys the ultrasound from the crystal to the tip and it cools the entire apparatus

At the generally used clinical power the tip temperature exceeds body temperature by only 1 2°C Because of this no heat is developed in the contact area with our apparatus—the risk of facial nerve lesions is lessened

The whole treatment head including the cable and cooling water pipes can be sterilized by boiling It is not necessary therefore to use sterile drapes during the operation

The conical tips are interchangeable and vary in diameter from 1 5 to 2 6 mm Bevelled tips have also been made *With such tips the surgeon can continually see the contact area in relation to the labyrinth as a whole*

The water inside the conical transducer conveys the ultrasound parallel with the walls and brings it to a focus just at the point (Fig 3) This is however not the source of ultrasound The source of the ultrasound is situated in the lead zirconate titanate disc

Intensities of more than 100 watts/cm² have been reached with this apparatus The maximum power output from the active front area of the transducer is presently over 4 watts The frequency of sound is 1 25 mc

Briefly our new Swedish apparatus is constructed as follows High frequency alternating current is transferred from the oscillator part to the transducer in which a small lead zirconate titanate disc covered with aluminium foil converts the electrical energy into ultrasonic waves

The beam is well concentrated in the conical treatment head The focus is situated immediately inside or just at the flat tip There is effective cooling by means of circulating water The temperature of the tip remains at about body temperature (1 2°C over that of the cooling water itself) The tips are interchangeable and vary in diameter from 1 5 to 2 6 mm in either straight or bevelled form

SCHLIEREN TECHNIQUE

By means of a special Schlieren technique or Dunkelfeldmethode the shadow of the ultrasound field can be reproduced photographically The wave motion resulting from the passage of the ultrasound through a medium will cause a change in the index of refraction due to sound waves The reproduction of the ultrasound will be radiate

The bunch of rays is well concentrated and consists of a strong central ray with weaker slightly radiating rays There is *no radiation from the sides of the transducer* a very important fact in consideration to the surrounding structures (facial nerve dura and brain) No shielding is necessary since this side radiation is totally missing

The penetrating power of ultrasound through bone of varying thickness



Fig 4

has been studied in order to obtain a rough idea of how far into the labyrinth the beam can reach

Flat bone slices (20 25 mm in diameter) were placed in the water tank in front of the transducer tip in the reflecting optical system

The bone is taken from the femoral diaphysis The thickness varied from 0 5 to 4 mm the power 1 2 watts the tip diameter 2 6 mm

With a bone thickness of 4 mm no ultrasonic penetration can be ... All radiation is absorbed and reflected 1 0 0 5 mm thick ... clear penetration but there is a strong reflection and absorption ...

This is in accordance with the clinical experience The ultra... trates bone thicknesses of 1 mm and less

The *apparatus* has been *tested experimentally* through the ... pigeons *Histological and functional changes were recorded* ... *with each other* *J Stahle* will give an account of these results in the ... lecture

CLINICAL APPLICATION

The technique of operation

At the ENT Clinic in Uppsala we have mostly followed ... with local anesthesia retroauricular incision and trans... followed by exposition of the labyrinth It is particularly ... convex surfaces of the horizontal as well as the vertical ... be exposed in order to give a good contact surface for the ... ducer In the beginning we thinned the bony labyrinth ... to the posterior part of the horizontal semi circular canal ... drill and 10 × 16 × magnification until the blue ...

visible, that is to say the labyrinth wall should be about 0.2–0.3 mm thick. This has prepared the way for the ultrasound to penetrate the bone without absorption or reflection.

During the last few years we began to prepare the contact surface further back towards the vestibule above and back of the horizontal semi-circular canal at the angle between the horizontal and superior vertical semi-circular canals (Fig. 4). (Arslan points out in his latest work that he has done the same thing.) By means of a diamond drill we grind out a small, rounded pit so that a good contact area is formed. The sound beam hereby comes into a little more certain contact with the otolith apparatus and the ampullae, but most important, we are working with the focussed beam in another direction further away from both the facial nerve and the cochlea. It is necessary to *thin the bone just enough to enable us to see in the microscope the soft, spongy contours of the enchondral bone* in the neighbourhood of the vestibulum.

At this point the labyrinth wall is about 0.3 mm thick and conditions are right for effective treatment. The ultrasound can penetrate the bone without too much absorption or reflection.

THE TECHNIQUE OF IRRADIATION

The transducer can now be applied. The transmission of the sound energy to the labyrinth is accomplished by means of a liquid layer which acts as a contact medium to the probe tip. Even the slightest layer of air between the flat tip of the transducer and the labyrinth bone can prevent the transferring of energy.

Under no conditions, however, must any liquid or blood be allowed to cover the convex surface of the horizontal semi-circular canal and reach into the middle ear or to fill the jugo-digastic area. It is most certain that ultrasonic transmission in such liquid layers could cause facial lesions.

Before application to the labyrinth a drop of saline solution should be attached to the tip of the transducer. In the operating microscope one can see the "microdrop" rise, be set into vibration and with remarkable ease become adherent to the probe tip when the ultrasound is turned on. The drop should be mixed with some blood and this suspension will then "couple" the probe tip and the bone of the labyrinth, thereby making the transmission of sound possible. Directing the beam towards the facial nerve and the cochlea can be carefully avoided with this technique. Every time without exception air must be maintained around the sides of the probe so that side radiation is avoided, and the probe must not touch the inner cortical bone or the exposed dura of the central cranial fossa.

In this "coupling" drop the sound transmission is good and the ultrasound can then be visualized as pulsating light reflexes and often as small standing waves in the blood around the tip of the probe, sometimes as a smokelike fog formation, dispersion of extremely small drops of fluid around the tip.

Through this visualizing of the ultrasound, we think that we have succeeded

in developing *a new irradiation technique* It permits us to direct the bunch of sound rays so that damage to the facial nerve and cochlea can be avoided to the greatest possible extent *We can see exactly where the sound beam enters the chosen target areas of the labyrinth*

Nevertheless an assistant keeps continual check of the facial nerve function and follows the nystagmus effect through Frenzel s glasses During the operation the nystagmus is registered electronystagmographically (registration of the displacements of the cornea retinal potentials is performed)

The irradiation is performed with intensities increasing from 20–40 watts/cm² corresponding to a power output of 1–2 watts from the tip The average irradiation time has been 32 minutes The longest time was 50 minutes the shortest 10 minutes The greatest dose was 5500 joules the lowest 800—the average dose being 2500 joules (1 joule=1 watt × 1 second)

The basic principle is to produce a homolateral irritative nystagmus with the ultrasound at first and finally bring forth a definite change over to a contra lateral destructive nystagmus the so called paralytic nystagmus

The length of the irradiation time is determined exclusively by the strength and duration of this homolateral irritative nystagmus

The irradiation is done intermittently for periods of 3–4 minutes with short pauses during which the apparatus is checked and a new drop of fluid is attached to the tip

After 10–20 minutes of irradiation the intensity of this irritative nystagmus successively lessens at the same time as the patient s nausea and giddiness are reduced—an indication of the lowering of vestibular excitability

The patient has now come to what we call the intermediary phase The eyes take up a somewhat indifferent position— they almost stand still — before the change over to the untreated side appears and we obtain a destructive type the paralytic nystagmus

The irradiation hereafter is done intermittently and we find that this so called paralytic nystagmus changes over to the irritated side time after time

This transitory direction change of the nystagmus has not previously been described and it indicates that there can be no assumption that a real destruction has taken place but should rather be considered a pseudo paralytic nystagmus *due to temporary loss of the vestibular nerve function on the irradiated side with a tonus preponderance from the labyrinth of the untreated side (perhaps an habituation or adaptation effect)* This transitory change of direction of the nystagmus must not be wrongly interpreted as a sign of destruction and thus cause too early a cessation of the irradiation

During all phases of the irradiation we have been successful in making electrical recordings of the nystagmus—the nystagmograms We have received accurate information on direction amplitude and intensity of the nystagmus *The operator* constantly gets an immediate analysis of the effect of the irradiation and he *does not cease until the change over to the untreated side remains definitely*

The duration of the irritative phase can be followed from perhaps 4-5 minutes to 40 minutes. One can see a very quick and strong homolateral irritative nystagmus, which after an intermediary phase, changes over to a definite paralytic destructive type beating towards the contralateral untreated side.

SUMMARY

Our present clinical experience can be summarized in the following points:

1. With *medicating* therapy crises of Ménière's disease are treated symptomatically. It is attempted to bring the stressed patient under psycho-somatic control and to a remission.

2. For malignant *double-sided* cases with permanent bilateral heavy loss of hearing one can discuss and resort to interruption of vestibular pathways with *streptomycin*.

3. For serious *invaliding one-sided* cases which do not respond to conservative therapy there is the *choice between labyrinthectomy, decompression and ultrasonic irradiation*.

4. Even if one critically takes into consideration the many years' duration of the disease and its natural tendency towards remission, the results of our *ultrasonic treatment* up to now have been encouraging.

The effectiveness of this irradiation, however, is completely dependent upon the technique and dosage used. It is possible to *preserve the hearing and to selectively eliminate or perhaps in most cases* considerably *reduce the vestibular excitability*, which in all our cases is usually *not tested with conventional methodics*. The results of all our caloric tests are based on electronystagmography done in partial darkness with the patient's eyes closed.

Reversible effect of ultrasonic irradiation has been observed. The caloric excitability to ice water has been eliminated for several months and has then returned in reduced form.

In the following lecture, Stahle will *demonstrate how we through careful analysis of the postoperative calorically induced nystagmus can clearly document the reduced caloric excitability*.

Stahle will also show the results of experimental irradiations of pigeon labyrinths, which demonstrate that one is hypothetically justified in presuming that *ultrasonic irradiation causes a degeneration of the secretory epithelium of the labyrinth. The disturbed function can thus be said to lead to a reduced secretion and thereby to a decreased labyrinthine hydrops*.

The results of our first clinical follow-up of 50 ultrasonically treated cases, 26 women and 24 men, show relief from or improvement in vertigo in 90 % (45 cases). Hearing is unchanged in 28 cases, improved in 6 cases, and impaired in 16 cases. Tinnitus is unchanged in 39 cases, improved in 11 cases. Only one case of facial paralysis, which was of a temporary nature, has been observed.

On the basis of all these experimental and clinical results we believe we are justified in proposing ultrasonic irradiation even in early invalidizing

cases of the disease, thereby giving the patient a good chance to find relief from crises of vertigo and possibly a slowing down of the progress of the disease and maybe by these means even a preservation of his hearing

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ELECTRONYSTAGMOGRAPHY IN MENIERE'S DISEASE BEFORE, DURING AND AFTER ULTRASONIC IRRADIATION[1]

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INTRODUCTION

Electronystagmography (ENG) permits qualitative as well as quantitative assessment of nystagmus. Duration and especially intensity (frequency, eye speed of the slow phase, number of beats, maximum intensity and total amplitude) can be measured with relatively great accuracy. A nystagmus too weak to be visible on direct inspection of the patient's eyes or through Frenzel's glasses can be recorded behind closed eyes.

At the Uppsala clinic we use the electronystagmographic technique advanced by Schott (1922) and Meyers (1929) and modified for clinical use by Aschan (1955) in which displacements of the cornea-retina potentials due to movements of the eyes are registered. A detailed account of the ENG apparatus and technique has been given by Aschan, Bergstedt & Stahle (1956).

The ultrasonic device and an extensive survey of its physical, physiological and clinical properties is given in a recent monograph by Sjöberg, Stahle, Johnson & Sahl (1963). The reader is referred to these two above mentioned books for further basic information.

Electronystagmographic examinations of patients suffering from Meniere's disease have been performed during many years at the Uppsala clinic. This paper will be a report of a greater material with special attention to the nystagmus induced by ultrasonic irradiation.

Before Irradiation

The electronystagmographic examination of a Meniere patient may give completely different results depending on whether the examination is made during an attack, immediately after an attack or during a vertigo-free period.

During an attack nystagmus is always present and can be of varying character. Earlier works (Aschan & Stahle 1957, Stahle 1958) have shown that the most usual types are direction fixed positional nystagmus (Nylén's type II) and true spontaneous nystagmus. Direction changing positional nystagmus (Nylén's type I) is less usual. In isolated cases a typical paroxysmal positional nystagmus has also been observed (Stahle & Terins 1963). The direction of the positional nystagmus does not indicate which side is affected (Stahle 1958).

[1] This investigation was supported by a grant from the Swedish Medical Research Council.
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TABLE 1

Maximum intensity	Duration		
	Normal	Pathological	Total
Normal	21	7	28
Pathological	25	19	44
Total	46	26	72

By the aid of ENG we found that in a few cases nystagmus has lasted up to 1 week after the culmination of the attack. This may indicate that the irritating condition in the labyrinth can remain considerably longer than is generally assumed (Aschan & Stahle 1957).

The *caloric test* can be normal or indicate a reduced excitability, directional preponderance or a combination of both these latter factors. The shorter the time between the attack and the caloric test, the greater has been the number of cases showing directional preponderance.

The incidence of so called canal paresis in advanced cases varies between 70–85 % (Cawthorne, Fitzgerald & Hallpike 1942, Cawthorne & Hewlett 1954, Stahle 1958). The incidence of directional preponderance has variously been given as 8–26 % (Andersen 1954, Cawthorne & Hewlett 1954, van Deinse 1946, Dix & Hallpike 1952). Combined lesions, according to Fitzgerald & Hallpike (1942) are common (Stahle 1958).

The effect of the caloric action is best evaluated on the basis of the intensity of nystagmus. This can be expressed in many ways: the culmination phenomenon (Torok 1948), the total number of beats, the total amplitude (Mittermaier 1954), the speed of the eye in the slow nystagmus phase (Henriksson 1956) or finally the *maximum intensity* (Stahle 1956, 1958). The maximum intensity is a mean value of the speed of the eye in the slow nystagmus phase during a ten second period at the peak of the reaction. We base our evaluation of the caloric reaction principally on the maximum intensity and only to a lesser extent on the duration. In some cases, however, the directional preponderance is best documented in the duration of the caloric reaction.

The unreliability of the duration is clearly shown in Table 1, in which the result of caloric reactions in 72 cases of Menière's disease is shown. 37 of these cases belong to a recent series examined before ultrasonic treatment, the remaining 35 cases refer to a previous series reported by Stahle 1958.

The evaluation of the caloric reactions is based on the difference in right-left sensitivity and we have applied the normal values from Stahle's earlier investigations (1956) to the formula suggested by Jongkees and co-workers (1962). The limits we have set up for the normal reactions take in duration *differences up to 10 % and for the maximum intensity differences up to 20 %.*

If the duration is taken as a starting point (Table 1), the caloric reaction is pathologically reduced in 26 cases. If the maximum intensity is taken, the caloric reaction is pathologically reduced in 44 cases, of which only 19 would be documented if duration were the criterion used. In 21 cases, finally,

the caloric reactions are normal both with regard to duration and maximum intensity.

A reduced excitability was thus found in about 60 % of the patients, a figure which is somewhat lower in comparison with those given in the introductory paragraphs. The explanation for this difference is that our actual material includes several early cases and reversible cases among which the caloric reaction can remain normal.

During Irradiation

Electronystagmographic recordings have been made as a matter of routine during the irradiation. Interference from other electrical equipment was eliminated after systematic grounding and shielding by means of a cathode follower input.

We have been able to document a homolateral irritative nystagmus during the irradiation followed by a contralateral paralytic at the very end of the irradiation. Three main phases in the nystagmus pattern can be differentiated (Fig. 1). (1) *The irritative phase* is the dominant one and is characterized by homolateral nystagmus of high intensity. (2) *The intermediary phase* is, according to Arslan (1958), a shorter nystagmus free interval following the irritative phase. Our experience has been that this phase is inconstant and if it appears it can be of very short duration—from 1/4 minute up to a few minutes. (3) *The paralytic phase* is the last one and is characterized by a contralateral nystagmus of moderate intensity. Its duration is from an hour or two up to 5–6 days.

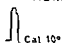
The intensity of the ultrasonically induced nystagmus, expressed as the eye speed of the slow phase, varies. The highest values have usually been noted during the first part of the irradiation. The intensity of the nystagmus during the irritative phase can be considerably higher than that induced during the pre-operative caloric test. This is probably due to the fact that the ultrasonic irradiation for the doses we normally use (1–3 watts) may be a stronger stimulus than a caloric test using either 30°C or 44°C water.

The intensity and direction of nystagmus during irradiation is illustrated in Fig. 2, which shows the records of a 30 year old man suffering from a left sided Meniere's disease. One minute after the irradiation was begun an intense left beating nystagmus having an average speed of 40°/sec was recorded (tracing No. 2). After about 4 minutes of irradiation the intensity had dropped considerably as shown by tracing No. 4. After 5 minutes of irradiation the nystagmus had changed its direction to the exact opposite, i.e. right beating with an intensity of 9°/sec (tracing No. 5) indicating the beginning of the paralytic phase. This right beating nystagmus still remained unchanged after 12 minutes of irradiation (tracing No. 6).

Nystagmus can change its direction from homolateral to contralateral several times during the ultrasonic treatment. This change of direction does not imply that the irradiated labyrinth is permanently destroyed, as has been previously maintained (Arslan 1953, 1956, and others). *The reversal is*

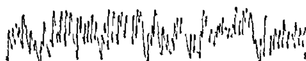
NYSTAGMUS DURING ULTRASONIC IRRADIATION

MENIERE'S DISEASE RIGHT EAR



IRRITATIVE PHASE

After 5 min



Paper speed 10mm/sec



Paper speed 25mm/sec

After 25 min



Paper speed 10mm/sec

INTERMEDIARY PHASE

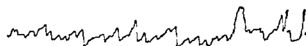
After 40 min



Paper speed 10mm/sec

PARALYTIC PHASE

After 45 min



Paper speed 10mm/sec

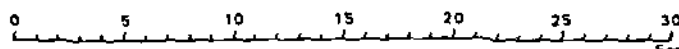


FIG 1 Case No 13 A 60 year old woman with a right sided Menière's disease The three main phases in nystagmus pattern during ultrasonic irradiation During the irritative phase nystagmus is right beating and during the paralytic phase left beating The intermediary phase is characterized by absence of nystagmus *The irradiation time in this case was 45 minutes, which considerably exceeds the mean value*

usually transitory and appears during the short pauses in irradiation which we usually make every 4–5 minutes in order to check the apparatus and change hands The stronger the homolateral ('irritative') nystagmus is, the stronger the following contra lateral nystagmus usually appears *This transitory after nystagmus has been called "pseudo paralytic"* (Sjöberg, Stahle, Johnson, Sahl, 1963)

After a time of irradiation varying from case to case no further homolateral nystagmus can be induced by ultrasound and the nystagmus becomes persistently contra-lateral *This last shifting of the direction can occur while irradiation is going on* and can take place during a time interval from 1/4 minute up to a few minutes This means that the intermediary phase can be

NYSTAGMUS DURING ULTRASONIC IRRADIATION

MENIERE'S DISEASE LEFT EAR

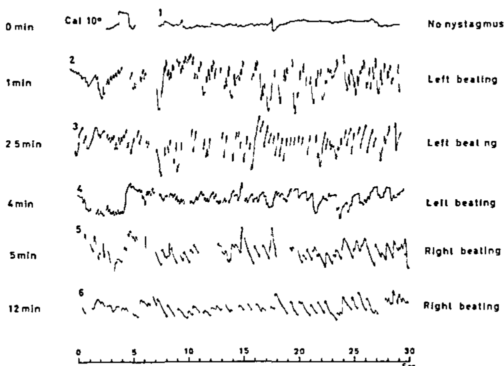


Fig. 2. Case No. 35. A 30 year old man with a left sided Menière's disease. During the first minutes of irradiation a brisk left beating irritative nystagmus (tracings Nos. 2–3) which gradually decreases in intensity (tracing No. 4). The paralytic phase commences in this case as early as 5 minutes after the beginning of the irradiation and is characterized by right beating nystagmus (tracings Nos. 5–6). Irradiation time 13 minutes.

insignificant. We have taken this persistently contra-lateral nystagmus as a sign of elimination of the labyrinth function.

However, caloric tests performed at follow up 10 days, 3 and 6 months or more after irradiation have shown that a complete loss of labyrinthine function (no reaction to ice water) is rare. A reduction of the excitability compared with the pre-operative tests has usually been achieved.

An example of transitory reversal of nystagmus is shown in Fig. 3, which illustrates a case of right sided Menière's disease. During the first part of the irradiation (tracings Nos. 2 and 3) a lively *right beating* irritative nystagmus is produced. In the following pause in the irradiation a weak *left beating* nystagmus, i.e. pseudo-paralytic nystagmus, can be seen (tracing No. 4). When the irradiation is resumed, a homo-lateral *right beating* nystagmus appears anew (tracing No. 5). In the next pause in the irradiation a contra-lateral *left beating* nystagmus can be seen again (tracing No. 6). After barely 17 minutes of irradiation a homo-lateral irritative nystagmus can no

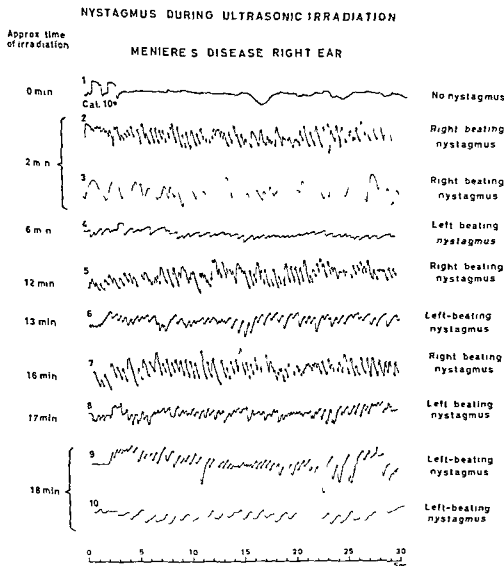


FIG 3 Case No 39 A 50 year old woman with a right sided Menière s disease Nystagmus can change direction repeatedly during the procedure The brisk right beating (irritative) nystagmus during the irradiation (tracings Nos 2, 3 5 and 7) is followed by transitory, weak, left beating nystagmus during short interruptions of the irradiation (tracings Nos 4 and 6) A persistent l ft beating nystagmus appeared in about 17 minutes of irradiation and has been interpreted as a sign of elimination of labyrinthine function (tracings Nos 8 9 and 10)

longer be elicited in this patient The nystagmus is hereafter definitely contra lateral, that is, left beating, and this is taken as a sign of elimination of labyrinthine function (tracings Nos 8, 9 and 10)

Ultrasonically Induced Nystagmus in Face Up and Face-Down Positions

Does the ultrasound affect the labyrinth in a similar manner as does calorization with hot water? There is reason for such an assumption as heat

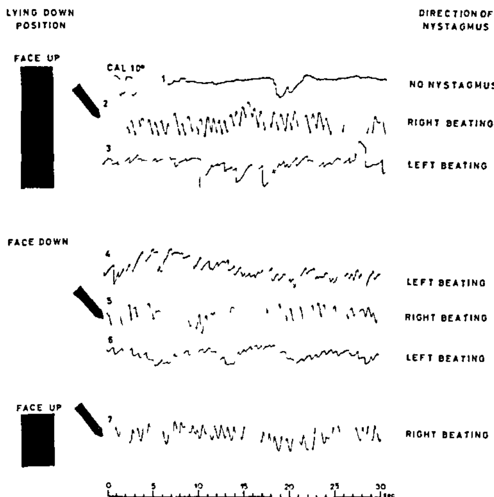


FIG 4 Case No 52 A 37 year-old man with a right sided Menière's disease Nystagmography performed in the operation theatre with the patient at first in face up (supine) position (tracings Nos 1–3) then in face down (prone) position (tracings Nos 4–6) and finally in face up position again (tracing No 7) The black arrows indicate irradiation

Before starting irradiation no nystagmus (1) During irradiation an identical brisk right beating nystagmus in face up (2) face down (5) and face up position again (7) During the short pauses following irradiation there appears a weak left beating pseudo paralytic nystagmus (3 and 6) Note that this last mentioned nystagmus induced in face up position (3) remains completely unchanged when the patient is turned 180° to face down position (4)

energy is emitted during the passage of ultrasound through layers of tissue with different acoustical impedance It has also been shown by several investigators that the tips of the Federici and the Bristol apparatus become very

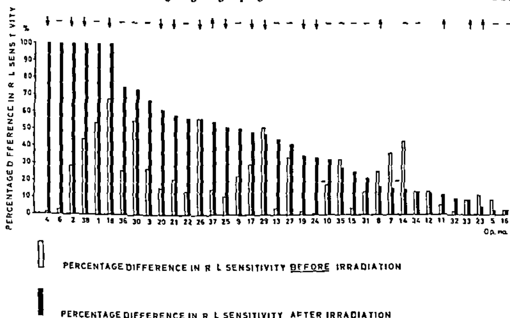


FIG 5 Diagram illustrating the caloric reactions in 37 Menière cases before and 2 months after ultrasonic irradiation The caloric reactions are assessed from the maximum intensity and not from the duration The normal limit to the allowed difference in right left sensitivity is at about 20 % (dotted horizontal line) Ordinate percentage difference in right left sensitivity abscissa patient number

The white columns show the percentage difference in right left sensitivity before irradiation and the black columns after irradiation The difference between the white and black columns in every single case shows the reduction in excitability due to ultrasound The 100 % post irradiative difference in right left sensitivity in the six cases to the left implies that the caloric sensitivity has been completely eliminated

↓ deterioration of hearing ↑ improvement of hearing — no effect upon hearing

hot (Angell James and co workers 1960 1963 Arslan and co workers, 1963) which causes a direct transference of heat to the labyrinth walls

Due to the cooling water circulating inside the Swedish apparatus the tip temperature rises only 1 2°C over that of the cooling water itself We can thereby maintain the tip temperature at about the same level as the body temperature and by that eliminate any chance of inducing nystagmus due to an excessively hot tip Thus there remains to try to analyze the effect of ultrasound as it passes through the labyrinth If one can assume that ultrasound should bring about a similar effect as that caused by heat energy from hot water at calorization then endolymph currents and nystagmus according to accepted rules should result This seems to be the case in rabbits (Arslan & co workers 1963)

In order to analyze the problem more thoroughly we have irradiated two Menière cases first in face up (supine) and then in face down (prone) position The ultrasound has been directed against the lateral semi circular

canal and the vestibule. *The result was a homo-lateral "irritative" nystagmus beating in the same direction despite the patient's position.* Furthermore, the "pseudo-paralytic" nystagmus, that is, the nystagmus following the "irritative" nystagmus, remained unchanged when the patient was turned from the face-up to the face-down position.

A recording made during the irradiation with the patient in different positions is shown in Fig. 4. The patient is a 37-year-old man suffering from a right-sided Ménière's disease. In the face-up position no nystagmus is noticed before irradiation. During irradiation—indicated by the black arrow—a lively right-beating nystagmus appears. When the irradiation is discontinued after 4-5 minutes, a weak transitory nystagmus in the opposite direction appears. This "pseudo-paralytic" nystagmus remained unchanged when the patient was turned 180° to the face-down position (tracing No. 4). During irradiation in this face-down position a lively right-beating nystagmus occurs (tracing No. 5). When the irradiation is broken off again after a few minutes, there appears, even in this face-down position, a weak contra-lateral "pseudo-paralytic" left-beating nystagmus (tracing No. 6). Finally, the patient is turned 180° back to the face-up position. Here the irradiation again induces a clear right-beating nystagmus, as can be seen from the lowermost tracing.

Ultrasound thus seems to produce a homo-lateral nystagmus during irradiation—no matter whether the patient lies in a face-up or face-down position. This is directly contrary to what happens in the caloric test with hot water. The results seem to contradict the fact that ultrasound should cause endolymph currents in accordance with Bárány's classic theory. It seems to be more likely that ultrasound causes a direct stimulation of the neuro-epithelium and the nerve cells, either thermally or mechanically, or in both ways.

After Ultrasonic Irradiation

In the days following the irradiation, most patients have a spontaneous nystagmus beating away from the irradiated ear. This "paralytic" nystagmus gradually disappears towards the end of the first week or sometimes earlier.

A thorough nystagmographic follow-up has been done two months after the irradiation of the first 37 cases treated. The caloric reaction (Fig. 5) has been completely eliminated in 6 cases and clearly reduced, in comparison with the pre-operative values, in 17 cases. Among the 14 remaining cases no significant changes in the caloric reactions were noted. The caloric reactions have been assessed from the maximum intensity only.

A typical example of reduction in caloric excitability due to ultrasonic irradiation is given in Fig. 6. The patient is a 36-year-old woman suffering from a right-sided Ménière's disease for six years. Before irradiation there existed a canal paresis visible only in the maximum intensity and not in the duration. Four months after irradiation the caloric reaction is further reduced, the difference in right-left sensitivity now being 75 %. This consider-

CALORIC TEST BEFORE AND AFTER ULTRASONIC IRRADIATION

MENIÈRE'S DISEASE RIGHT EAR

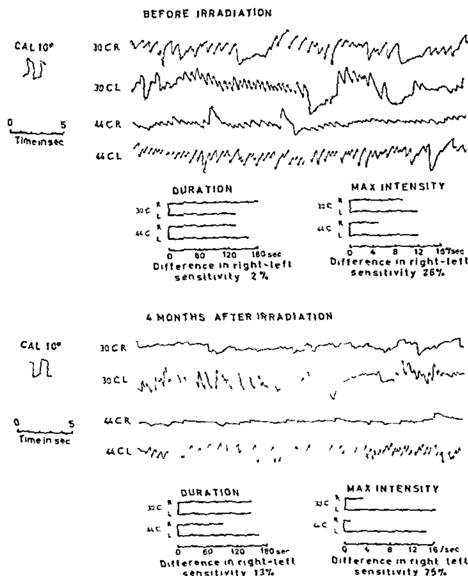


Fig. 6. Case No. 40. A 56 year-old woman with a right sided Menière's disease. The *reduction of* the caloric excitability due to irradiation is clearly visualized by the four lowermost curves. The unreliability of judging the [illegible] ction on the basis of the duration is clearly *apparent as* well as the superior merit of [illegible] the caloric reaction on the basis of the maximum intensity

able reduction of the labyrinthine function however is not reflected in the duration but only in the intensity of the reaction This case clearly supports statements made previously (Stahle 1958) and in the introductory paragraphs—namely that the duration is a most uncertain measure of the labyrinth function

The caloric excitability can *temporarily* be completely eliminated or be reduced Cases have been observed in which the caloric reactions have been missing for 3 4 weeks following irradiation after which time the excitability has returned to a varying extent An example of this is given in *Acta Oto laryngologica* Suppl *178* p 63 Fig No 50

COMMENTS

It is very important to study the *caloric reaction* in cases of Menière s disease as this reaction will give an objective measure of the effect of the ultrasound upon the labyrinth Judging from the literature it would seem that the caloric test is to a certain extent neglected and the results of the treatment are judged exclusively according to the patient s subjective statement The caloric reaction is best assessed on the basis of the intensity of the nystagmus and in addition to that nystagmography in some form is essential

The methods which are nowadays in greatest use namely electro nystagmography according to Schott Meyers or electro oculography according to Torol Pfaltz Richter are very sensitive and can register a nystagmus too weak to be seen on direct inspection or through Frenzel s glasses This means that a weak reaction on the records could have been missed if conventional non nystagmographical techniques were used

Among the 37 cases on which follow up investigations have been performed the caloric reaction after ultrasonic irradiation was completely eliminated in 6 cases all of which had shown clear reactions before the treatment In 4 of the cases the reason for this caloric areflexi may be that during the thinning of the bony wall a minimal fistula appeared in the semi circular canal The membraneous labyrinth was undamaged In these cases the inner ear has been exposed to too much ultrasound resulting in total deafness and caloric areflexi In the remaining two cases this can not be the explanation

It is known through Meurman s investigations (1951) that a therapeutic fenestration in Menière s disease results in a further reduction of hearing and in a reduction of caloric excitability but not in a complete elimination of the inner ear function On the other hand if the membraneous labyrinth is damaged were it only through a minimal tear (Cawthorne 1963) a total elimination of the inner ear function will result The reason for the complete elimination of the inner ear function in the four cases mentioned above must therefore have been due mainly to the ultrasound and not only the surgical trauma

The ultrasonically induced nystagmus in the face up (supine) and face down (prone) positions are identical in appearance This has not been

observed previously, and it gives occasion to reflections as to the manner of action of the ultrasound Our observations contradict the theory of thermally provoked endolymph currents similar to those produced in the caloric reaction The ultrasonic waves transmitted through the peri and endolymph must work more directly upon the neuro epithelium If the principal effect is thermal or mechanical cannot yet be determined For the present one must assume that both manners of action—and possibly even others—are relevant Research into this has been initiated The problem will also get a wider aspect owing to the fact that we have shown that ultrasonic stimulation of the labyrinth can induce nystagmus which does not follow the classic laws as set up by Barany

Our results are contrary to those reported by Arslan Sala & Molinari (1963) who in animal investigations have shown that ultrasonically induced nystagmus will change its direction in an exactly similar way as calorically induced nystagmus when changing the position of the head Their explanation is that the heat from the tip of the Federici apparatus causes endolymph currents In experiments with cold irradiation where the tip of the transducer was cooled down they succeeded after 2–20 hours of irradiation in eliciting a nystagmus in rabbits which was not reversed when the position of the head of the animal was modified The explanation for this last mentioned nystagmus should be that there is a direct ultrasonic effect upon the neuro epithelium It is however difficult to understand why this should take such an extremely long time

The transitory reversal of the ultrasonically induced nystagmus calls for an explanation This type of phenomenon can be observed on more than one occasion for example labyrinthine fistula (Aschan Bergstedt & Stahle 1956) caloric tests and in connection with paroxysmal positional nystagmus In the latter condition a weaker nystagmus in quite the opposite direction can in some cases be recorded with the patient still in the critical position after the violent paroxysm of nystagmus has passed off (Stahle 1961 Stahle & Terins 1963) The most plausible explanation for this phenomenon is that the primary stimuli (ultrasound calorization change of position) are very powerful and will temporarily paralyze one labyrinth to a varying extent in which case the non stimulated labyrinth will temporarily dominate

SUMMARY

Electronystagmography provides valuable help in diagnosis follow up and documentation in cases of Meniere's disease It makes possible the discovery of a very slight nystagmus which might have been overlooked with conventional methods of investigation It facilitates an analysis of the intensity of the caloric reaction which is a much better expression of labyrinthine function than is the duration

The nystagmus pattern during ultrasonic irradiation has been mapped out electronystagmographically Three main phases have been documented A transitory reversal of nystagmus is described Ultrasonic irradiation in most cases results in a

reduction of the caloric reaction, whereas a complete areflexia is rare. Temporary areflexia is described. Irradiation with the patient in supine and prone position has elicited identical nystagmus. This has been interpreted as a sign of direct stimulation of the neuro-epithelium and will thereby contradict the theories of calorically provoked endolymph currents.

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POSITIONAL NYSTAGMUS IN MENIERE'S DISEASE

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I was asked to give a report about positional nystagmus during Meniere's attacks. We treated nearly 150 patients with Meniere's disease in the last 2 or 3 years, but only a few of these patients showed attacks during their stay in hospital. So I have to apologize for not being able to add anything more of value to this problem. Particularly the observations made by Aschan and Stahle of a direction changing positional nystagmus during the attacks seem to be rather important and I think it would be of utmost interest to hear more about this phenomenon, which might convince us to believe in a central origin.

In many points I agree with Jongkees concerning the psychological aspect of Meniere's disease although I am not quite so sceptical about the treatment.

We always began with diuretics, nicotinic acid, vitamins A and E, blockade of the sympathetic nerve. We also used i.v. injections and more and more infusions of novocain. In these cases the hearing improved in more than 60 %. The same occurred with the tinnitus; vertigo disappeared also in more than 60 %.

Only in 12 % we had to use the ultrasonic treatment. In 5 cases we removed the horizontal semicircular canal.

72 of our patients had a complete recruitment; 50 of these patients showed an improvement of hearing after conservative treatment. Out of the number of 25 patients with uncomplete recruitment only 7 reacted with improved hearing, whereas the other 18 patients remained uninfluenced. It may be that *cases with complete recruitment permit a better prognosis than cases with uncomplete recruitment.*

27 patients showed spontaneous nystagmus to the affected side, 12 patients to the *non* affected side. We gained the impression that better results are to be obtained in the first mentioned cases.

For further details see the report published by G. Rossberg, H. Schilffarth, K. Henning and I. K. H. Beck: Zur Diagnose, Therapie und Prognose der Menièreschen Krankheit. *Zeitschrift Laryng. Rh nol.* 42, 5, 316 (1963).

THE CALORIC TEST IN MENIERE'S DISEASE

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Since we use the combination of electronystagmography and caloric test routinely in our department, we are sure that the speed of the slow phase of nystagmus is the best indicator to show the reaction of the vestibular organ. A second point very important for the evaluation of the caloric test is the fact that normally the reactions to the caloric test are extremely diverse even if the stimulation is neatly standardized as in Hallpike's procedure.

The differences in normal persons, both for directional preponderance and for difference in excitability, were significantly greater in absolute numbers in highly excitable labyrinths than for those which have a low level of excitability.

Using the test of Wilcoxon we could prove that a correlation exists between the total excitability of two labyrinths and both the magnitude of the difference in excitability between left and right and directional preponderance.

For this reason it seems necessary to express both in a percentage of the total excitability of the two labyrinths. If 1 is left cold, 2 right cold, 3 left hot and 4 right hot, the difference in excitability is expressed in the formula

$$\frac{(1+3)-(2+4)}{1+2+3+4}\times 100\ \%$$

and the directional preponderance as

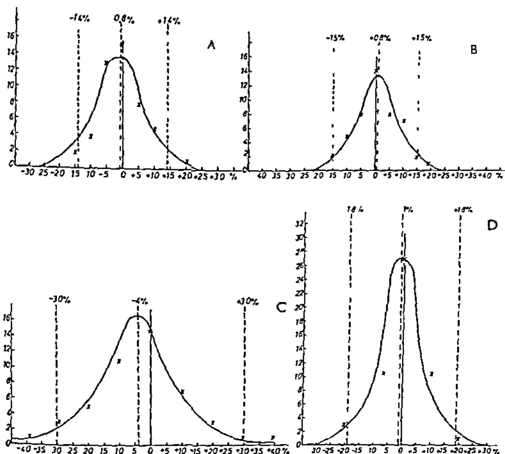
$$\frac{(1+4)-(2+3)}{1+2+3+4}\times 100\ \%$$

The standard deviation from the mean value was calculated in a large number of normals. We think the limits of normals are given by twice the standard deviation.

For a difference in excitability this proved to be $\pm 14\ \%$ for duration and $\pm 15\ \%$ for the speed of the slow phase of caloric nystagmus. For directional preponderance the numbers were $\pm 30\ \%$ for duration, $\pm 18\ \%$ for the speed of the slow phase (Fig. 1).

Hamersma has well proved that the test with water of 30 and 44°C (Thornval 1917, 1932), Fitzgerald & Hallpike (1942) is clearly superior to other tests (Kobrak 1922, Veits 1928).

In an e.n.g. examination of 255 patients complaining of vertigo 149 did not show a spontaneous or positional nystagmus. In 4 of these, i.e. 3 %, a pathological directional preponderance was found, in 2, i.e. 1½ %, a difference in excitability could be shown. In all the other cases a spontaneous or positional nystagmus was present. The 6 cases mentioned here did not belong to the group of sufferers from Menière's disease.



A–B, Difference in excitability of the two labyrinths C–D, Directional preponderance A and C for the duration of the nystagmus B and D for the speed of the slow phase The spread of the findings in 47 normals is given, the number of cases against the percentage The mean value and the limits of normality (twice the standard deviation) are indicated

Therefore we may conclude, I think, that the caloric test is not necessary to strengthen the diagnosis of Menière's disease when perception deafness with recruitment is found, as e.n.g. will give us the information about the pathology of the vestibular organ much more easily and quickly The result of the caloric test cannot teach us more about the clinical picture of the disease either

To my opinion the caloric test, time consuming as it is, can only be valuable to those who do not have the possibility to resort to electronystagmography for the examination of patients, suffering from Menière's disease

As a matter of fact, it may still be very useful for the differentiation of other causes of vertigo In these cases (e.g. central deviation, pathology of the nuchal vertebrae, vestibular neuritis, acoustical neurinoma) the caloric test can be of great value

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SURGICAL TREATMENT OF MENIÈRE'S DISEASE

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Many treatments, either surgical or medical, were proposed for Menière's disease. Surgically, most of the operations result in the destruction of the organ, but when the ear still shows a certain degree of hearing, this operation is not to be recommended.

For many years, various authors have come to think that the typical Menière's disease—maybe partly only, but evidently—has provoked a labyrinthine hydrops.

From his own experience—animal experiments, and clinic observations started even before 1927—Georges Portmann has compared some cases of Menière's disease to the glaucome of the eye. This fact has been confirmed ever since, and more particularly by Hallpike's and Cairn's excellent histo-pathological findings in 1938.

From their studies physiologists have demonstrated various points of secretion, and the role of resorption for the endolymphatic liquid of the endolymphatic saccus. Therefore, when the mechanism of secretion or resorption is going wrong and gives a hypertension of the endolymphatic fluids, it looks logical to make the opening of the endolymphatic space.

The endolymphatic saccus seems to be the most adequate site of this opening: (1) because it is the physiological point of fluid resorption, (2) because it is easily accessible through the mastoid bone, (3) because its opening is absolutely safe for the hearing, as it stays far away from the neurosensorial end organ. We know that it will not be the same if we open the endolymphatic space on another place (1/2 circular canal or utricula).

The opening of the endolymphatic saccus for endolymphatic hydrops has been described in 1927 by Georges Portmann. The operation is simple and can be performed with the classical instrumentation of the otological surgery, it has been described many times and is made up of the following steps:

(*a*) retro auricular incision,

(*b*) opening of the mastoidian bloc behind the external auditory canal and the antrum,

(*c*) opening of the posterior wall of the petrous bone behind the posterior labyrinth: the lateral sinus is shown, the endolymphatic saccus is discovered forward the latter.

(*d*) opening of the endolymphatic saccus.

After this operation follows immediately a rough decompression of the endolymphatic liquid.

The symptoms, and particularly the vertigos, fall back during the following week and the experience relates lasting results.

We do not know whether the opening of the saccus is kept on, but the results stated are generally permanent. In order to keep this opening securely some authors have modified the operation. Naito (Osaka, Japan) uses a special flap to keep permanent the opening between the endolymphatic saccus and arachnoid spaces. William House (Los Angeles, USA) inserts into the opening a silicon, polythene or teflon shunt which secures a permanent communication between saccus and arachnoidian spaces.

These modifications are logical but we still do not know whether they are absolutely necessary, as our results with the original techniques are excellent.

Out of a series of 80 cases we get 93 % of long term success for the vertigo, 32 % improvement of the deafness, 30 % improvement of the tinnitus. For this reason, and when the patient has not favourably reacted to the medical treatments, and when his ear still shows a certain degree of hearing, *we keep going on with this type of very soft physiological surgical operation.*

We are not very keen to change again our method with another one like the destruction by ultra-sound proposed by Arslan. It looks also a good principle to destroy selectively the vestibular end organ but are we sure that the ultra-sound wave is always sent to the exact place and not to a wrong one like the facial nerve in the Fallopius canal?

To conclude, I want to emphasize 3 points.

1. We must never forget that the typical Menière's disease generally is a local consequence of some general (organic and psychologic) disorders; this is the reason why we prefer, first of all, the medical treatment. With the help of a good internist, the great majority of cases are cured or sufficiently improved.

2. If the patient cannot be sufficiently improved by medical treatment and if we are dealing with a typical peripherical Menière's disease with a certain degree of hearing, we use the "drainage of the saccus", that is to say Portmann Senior's operation, without or with Naito's or House's modifications.

3. If the patient shows a total or nearly a total deafness of the ear affected with Menière's disease, we use the surgical destruction procedure through the oval window, the approach being similar to the one of the stapes surgery as described this morning by Cawthorne.

OPERATIVE TREATMENT IN CASES OF MENIERE'S DISEASE

Own method

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The operative method I have used in cases of Meniere's disease intends to eliminate the vertigo and tinnitus symptoms or at least to diminish them to the point of absence of discomfort and at the same time protect the residual hearing. The surgical procedures which have been in use and of which Cawthorne's method is the most popular and frequently adopted comprises a more or less severe destruction of the labyrinth and hearing will completely disappear.

In accordance with the principles presented the operation consists of the following parts:

1. relieving of the intra-labyrinthine pressure through the fenestration operation.
2. tamponade of the vestibule and the ampulla portion of the horizontal semi-circular canal without damaging the membranous labyrinth.
3. attempts to influence tinnitus through (*a*) tympanosympathectomy and (*b*) cutting the corda tympani nerve to prevent sound impulses coming through these nerves to the labyrinth.
4. cutting the tensor tympani muscle tendon and the stapedius muscle tendon to prevent roaring or buzzing noises which could arise by a strong tonic contraction of these muscles.

My material consists of two series of cases, the first one being done 1950–1954, the second 1954–1958. Thus the time of observation will be at least five years.

In the first series for tamponade of the semi-circular canal I used small wedge-shaped pieces of cartilage taken from the cartilage of the concha. As I in spite of taking great care not to damage the membranous labyrinth got impairment of hearing in about 50 % of the cases, I substituted the tamponade material with a filling substance similar to the one used by dental surgeons for the filling of tooth cavities.

In earlier papers I have reported on 58 cases operated according to the first method. In doing so I was able to demonstrate that hearing was unimpaired in about $\frac{1}{3}$ of the cases, while the tinnitus had been considerably reduced in about 75 % of the treated cases.

If I now summarize the total number of cases, nearly a hundred, it will appear that the results with the filling substance had not been any better than the other ones.

In all the cases the vertigo sensation is practically gone, the preoperative hearing remains in almost $\frac{1}{3}$ of the cases and the tinnitus has been somewhat reduced in roughly $\frac{2}{3}$ of the total number of cases.

The ideal for a successful Menière operation in my opinion is a non dangerous procedure that will bring about alleviation of the troublesome symptoms of vertigo and tinnitus or at least their reduction to such a degree that they do not disturb the patient and the simultaneous preservation of hearing Sometimes hearing is worthless and may then be sacrificed which is stressed by many authors In many cases however the Menière symptoms may be severe and troublesome for the patient although hearing is relatively good constantly or remittently In these cases it is unquestionably desirable not to undertake a therapeutic procedure which will mean a complete destruction of the sense of hearing In cases of bilateral involvement operative treatment may be considered if hearing can be preserved but on the other hand surgery is inconceivable if hearing anyhow probably will be destroyed

As since a few years I have retired from my hospital work I have not had the possibility to fulfil the scheme of operations after the above mentioned principles Anyhow I sincerely hope that someone else will adopt the indicated idea and perhaps find a method of tamponade or other kind of blocking the vestibular apparatus that will free the patient from his subjective symptoms but a method that will enable us with reasonable certainty to promise the patient unimpaired hearing

If the now very popular treatment with ultrasonic waves should solve the problem surgical intervention in case of morbus Menière will of course be quite unnecessary

STUDIES IN THE MEASUREMENT OF ULTRASONIC ENERGY AND ITS EFFECT ON NERVE TISSUE

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In the course of developing a new ultrasonic transducer and generator for the Royal Ear Hospital animal experiments were performed on cats and cattle using the brain in the former and the inner ear in the latter. Dosage was measured by calorimetric and Schlieren techniques but radiation pressure using a submerged balance provided a much simpler and more reliable method. The new transducer was designed to be usable for irradiating the anterior pituitary by the sphenoidal route. An ultrasonic transducer for neurosurgery has also been developed and this has been used to establish the anatomy of the brain as well as to destroy tissue. Both types of transducer are provided with a simple tuning indicator and power level meter so that the function of the crystal is monitored throughout its use.

The large difference between the power level needed to produce lesions in brain compared with the small power that suffices in the vestibule is thought to be due to the bony canal acting as a wave guide. This is thought to explain the reported variability in results through the effect of interference.

In view of the instability of the ultrasonic generator developed in Italy for Professor Arslan it was decided to develop a new pattern for use at the Royal Ear Hospital University College Hospital London in 1959.

The early unsuccessful attempts to provide a satisfactory instrument were reported to the third International Conference of Medical Electronics held in London in July 1960. It was not until January 1961 that by good fortune it was possible at the eighth attempt to provide an instrument that was capable of being sterilised by autoclave that operated at low voltages and which did not develop heat close to the tissues.

Before considering the use of the new instrument on patients it was considered essential to carry out trials on animals not merely by direct application to the cerebral hemisphere but by application to the semicircular canal. For this it was necessary to employ an animal with a petrous temporal comparable in size and anatomy with the human.

Studies were made through the co operation of the Royal Veterinary College London and it was decided that domestic cattle provided the closest approximation. Mr I Angell James of Bristol has carried out a large number of operations on sheep but the anatomy differs and the size is significantly less. The cost is of course more reasonable. It has been stated that the lion and the giraffe are closer still but neither can be seriously considered as laboratory animals.

Glaxo Laboratories Ltd. very kindly put at our disposal a heifer and the operation was performed at their experimental farm. The operation was performed under general anaesthesia and an attempt was made to record the eye movements by electro-oculography. Unfortunately the anaesthesia prevented nystagmus from being observed and it was necessary to rely on dead reckoning based on the dosages then being used on patients, Angell James' calorimetric measurements being used as the basis.

The measurement of dosage had already been considered very fully and through the co-operation of the Physics Department of Bristol General Hospital tests have been carried out using their calorimetric and Schlieren techniques. These methods were considered unsuitable for use in a hospital without a physics department versed in ultrasonic techniques and after a visit to Massachusetts General Hospital, Boston, it was decided to employ radiation pressure as the basis of measurement.

The commercial ultrasonic intensity meter used in Boston recorded on a scale calibrated up to 40 watts. This was quite unsuitable for the low powers used in otology so a much more sensitive device was developed in the form of a completely submerged balance, the position of the arm being observed by a telescope with a graticule some distance from the tank containing the balance. This device has become widespread in otological departments and its results tally well with those of the calorimetric method (Fig. 1).

The original Arslan transducer had a diameter of 5 mm giving it an area of 0.2 cm². An intensity of 4 watts per cm² therefore meant that the total acoustic power was 0.8 watts. The original Royal Ear Hospital transducer consisted of a copper cone the tip of which was open giving an internal diameter of 3 mm and an external diameter of 5 mm. It was considered wiser to employ the same total power of 0.8 watts rather than to attempt to match the intensity per square centimetre.

As all later instruments in this field have employed much smaller active areas than the original Arslan machine it has become rather unrealistic to describe dosage in terms of watts per square centimetre and it is suggested that in all cases the total acoustic power and the dimensions of the active area should be given when publishing reports. Unquestionably the intensity varies very greatly in different parts of the active area but while all the acoustic power is of importance when the heating effect is considered, only that delivered to a site where the bone thickness is less than one millimeter is likely to have any effect on the vestibular apparatus.

As Angell James was at that time irradiating with intensities of the order of 0.8 watts at 1 megacycle for about 20 minutes the same duration was employed on the heifer. The animal was allowed to survive for three weeks and was then sacrificed using intra vitam fixation. The Ferens Institute very kindly performed the histological examination of both temporal bones which show very complete destruction of the epithelium in the canals, relatively slight damage to the nerve cells of the vestibule and least damage to the organ of Corti (Figs. 2 and 3).

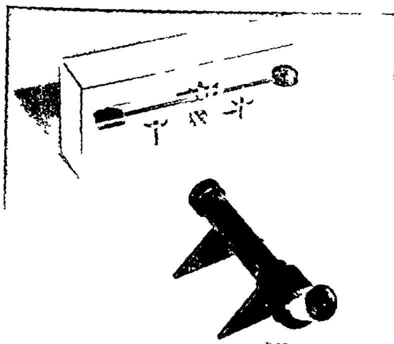


Fig. 1. Radiation pressure balance for measuring the intensity of ultrasound. Intensities as small as 0.007 watts can be measured.

At that time a similar dosage was applied for a similar period to the cortex of the cat after craniotomy but through the dura. Only the very slightest evidence of ultrasonic damage was recorded.

Since then very considerable improvements have been made to the transducer and generator and the apparatus has had considerable use on patients. The transducer is now provided with a system of interchangeable applicators so that the same crystal can be used to irradiate for different purposes. The applicator usually used for Menière's disease has a diameter of 2½ mm with a long tapering cone that gives the surgeon the best possible power to observe the point of application (Fig. 4).

No protection is provided round the tip as it was felt that this would obscure the surgeon's view. It is, however, necessary to suck out the irrigating saline down to a level close to the tip as otherwise the ultrasonic energy tends to diverge too soon. Tests with a small piezo-electric probe show that even when immersed in water the power level round the tip of the applicator is only 1% of that emerging from the tip. With the 2½ mm tip it is possible to obtain as much as 5 watts of power before cavitation occurs. This represents an average of 100 watts per square centimetre.

This abundance of power is never required for Menière's disease but it has its application when a longer applicator with an 8 mm diameter tip is used for the irradiation of the anterior pituitary. With this applicator 10 watts of power distributed over an area of 0.5 cm² gives an average of 20

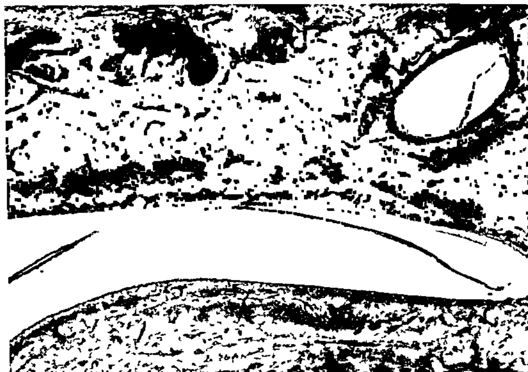


FIG 2 Longitudinal section of the lateral semicircular canal and transverse section of posterior semicircular canal three weeks after 10 minutes irradiation with 0 8 watts (Heifer)

watts per cm² and enables the whole pituitary to be uniformly irradiated in a single field by the sphenoidal route

While this development of the transducer was occurring comparable improvements were made in the generator which now has a simple tuning indicator in the form of a cathode ray tube The correct tuning is indicated at a glance when the pattern on the face of the tube is a straight line and not a loop This tuning indicator is of particular value as the pattern changes immediately any air enters the path between the crystal and the applicator tip

Without the tuning indicator, errors of 200 % were possible in the meter readings but using the tuning indicator the error between room temperature and body temperature is only 10 %

Air is the perpetual enemy of ultrasound transmission in all the medical applications and it is quite possible in any of the designs for air to be present in the transmission path so that the surgeon is misled as to the actual dose being received by the patient

Parallel with the experiments for the ultrasonic surgery of Menière's disease a series of experiments were performed on the brain of the cat using a true focussing technique This is a development of the techniques used at the University of Illinois the University of Iowa and at Massachusetts General Hospital The elaborate installations at these centres employ quartz crystals with high operating voltages and in all cases elaborate control systems demand the services of an ultrasonic physicist



FIG 3 Vestibular region of the same animal

Comparable developments using the modern lead zirconate titanate crystals in the form of concave bowls have resulted in the development of a simple and comparatively cheap installation that permits the production of small focal lesions deep in cat brain with no lesion between the cortex and the focus Ultimately it is proposed to apply the technique to patients at the West End Hospital for Neurology and Neurosurgery London for the surgery of Parkinsonism and even more important in the destruction of tumours The technique is of particular value already in neuro physiology and in neuro pharmacology and an equipment is now under construction for the Smith Kline & French Laboratories of Philadelphia

It is conventional to describe the size of the focus of such a transducer in terms of the size of the zone within which the intensity is not less than half the intensity at the point of maximum intensity As in fact the dosage needed for cell destruction has to be controlled to a much better accuracy than 50 % there is the paradoxical result that lesions much smaller than the computed focus are readily obtainable At the Massachusetts General Hospital it is possible with close attention to all factors to obtain lesions as small as 50 nerve cells and to locate these stereotaxically well enough for the lesion to be found without excessive histology

Considering the advanced state of ultrasonic diagnosis it is surprising that no attempt has so far been disclosed of using the same transducer to diagnose the exact internal anatomy of the organ and also to produce destruction of

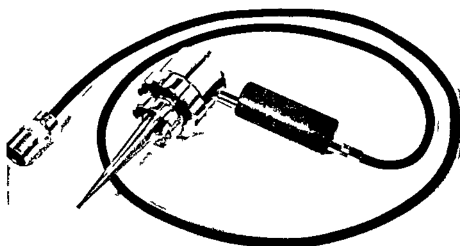


Fig 4 The Royal Ear Hospital transducer with the 2½ mm applicator used in Menière's Disease

focal areas within it This has recently been done at Paddington General Hospital on the cat The focussed transducer when used with the flaw detector apparatus used in diagnosis gives an extremely high sensitivity in the axis for a few millimeters above and below the focus but is insensitive to echoes from any other area With this it was possible to demonstrate the width of the gap between the hemispheres of the cat through the unopened dura This technique will be developed further and extended to the eye as an alternative to the photo coagulator

A worker bridging the fields of otology and neuro surgery is struck immediately by the remarkable difference in power levels While the American workers in neuro surgery are measuring their dosage in terms of kilowatts per square centimetre the otologists are using intensities as low as one watt per square centimetre attenuating it by passing it through bone deflecting it round the curve of the canal and still obtaining demonstrable effects on nerve tissue

Being struck by this paradox the experiment of applying the transducer direct to the cortex of the cat was repeated using both the 2½ mm and the 8 mm applicators at 0 4 watts and 10 watts total power or 8 watts per square centimetre for the 2½ mm applicator and 20 watts per square centimetre for the 8 mm applicator In each case exposure was continuous for 10 minutes At 8 watts per cm² only a superficial vesicle was produced where presumably the intensity was above the average level (Fig 5) At 20 watts per cm² a wide area of necrosis was produced 7 mm in diameter and penetrating 7 mm into white matter but only 4 mm into the more resistant grey matter (Fig 6)

The paradox can only be explained on the assumption that in the semi circular canals the endolymph retains the ultrasound by internal reflection from the wall so that in effect the same ultrasonic energy passes any given nerve cell many times while in the cat brain it only passes the cell once

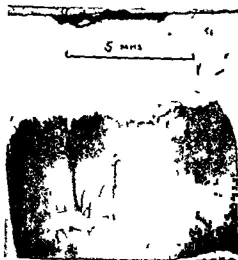


Fig 5



Fig 6

Fig 5 Cerebral cortex of cat sacrificed 24 hours after irradiation for 10 minutes at 8 watts per sq cm with applicator 2½ mm in diameter

Fig 6 Cerebral cortex of cat sacrificed 24 hours after irradiation for 10 minutes at 20 watts per sq cm with applicator 7 mm in diameter

The complex situation that exists within the endolymph space when ultrasound is passing both ways round a closed loop must be quite impossible to compute Considerable interference must take place between the various reflections from the inner walls but particularly when the clockwise energy meets the anti clockwise energy Angell James has suggested that shear waves play an important part in the effect on nerve cells but it seems difficult to believe that the angulation of the rays in the fluid to the bone surface would be sufficiently great for this conversion to occur anywhere except close to the point of entry on the lateral canal In this case by the time the receptors were reached the shear waves would be heavily attenuated

It is vain to speculate too much when objective proof seems unobtainable *There are however two important points that are of clinical value to the* surgeon that arise from these observations

Assuming that the only energy that has a useful clinical result is that which is transmitted by the endolymph from the fenestra to the receptors it appears to be a matter of chance whether the receptors will in any particular case lie at a node where there is hardly any activity or at an antinode where there is maximum activity As the wave length of even a 3 megacycle wave is long compared with the individual cell the frequency does not seem likely to affect the position very much At the higher frequency attenuation in bone is greater but transmission along a narrow canal is also easier To avoid the sparing of receptors by the standing wave phenomenon it is advisable for the surgeon to avoid keeping the applicator tip always angled the same to the canal but it should be slightly tilted anteriorly and posteriorly

without altering its point of application Quite a small variation in angle should suffice to move any remote nodal points considerably This is the likely explanation of some cases where no nystagmus is elicited from a properly functioning transducer

The other point is the risk of cochlear damage Wide discrepancies in the amount of hearing loss after ultrasonic irradiation have been reported even within the experience of a single surgeon This appears to be attributable to the importance of the physical dimensions and angulation between the *opening of the bony canal of the cochlea into the vestibule* Quite minor variations in alignments would account for very variable proportions of the available energy entering the cochlea This is clearly beyond X radiology to establish in advance and all that can be done is to give a guarded prognosis for the cochlear function

Acknowledgment is made to Myles Formby F R C S Surgeon to the Royal Ear Hospital who has been in charge of the clinical side of the work and who operated on the heifer to Professor R S Pilcher of University College Hospital and Dr A Beck of Paddington General Hospital for providing facilities for animal experiment to the Ferens Institute and Dr H C Grant of the West End Hospital for Neurology and Neurosurgery and to Glaxo Laboratories for providing the heifer and operation facilities at their farm

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HISTOLOGICAL EFFECTS OF ULTRA SOUND ON THE LABYRINTH OF THE SHEEP

G A DALTON
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Mr George Dalton Birmingham gave an account of some of the animal experiments of Mr Angell James and their co workers in Bristol He said

One of our aims has been to apply the technique used in the treatment of Meniere s disease to an animal whose labyrinth approximates in size to that of the human being Of the common domestic animals the sheep most nearly meets this criterion The over all antero posterior dimension of the labyrinth is 14 mm in the sheep and 17 mm in man

We have carried out altogether some twenty irradiations in the sheep using in the first seven cases the modified Federici 1 megacycle/sec apparatus and in the remainder the 3 or 5 megacycle Bristol apparatus and in all cases using the continuous saline irrigation technique

We have employed general anaesthesia which was administered through an endotracheal tube but otherwise the apparatus and technique have been exactly the same as in the treatment of the human patient

The approach to the sheep s lateral semicircular canal is through a post auricular incision There being no mastoid antrum in the sheep the lateral semicircular canal has to be identified by following up the vertical portion of the facial nerve from the stylomastoid foramen to the junction with the horizontal portion of the nerve Cautious burring above and behind the bend in the nerve reveals the grey line of endosteum of the lateral canal

The ultra sound treatment head is now applied to the lateral canal as in the human (The sequence of irritative nystagmus and reversal to paralytic nystagmus during treatment in sheep was shown in a film together with the post operative effects on the animal)

Five of the animals died within a few days of the operation and post mortem examination by veterinary colleagues suggested that death was due to stress with adrenal failure

Histological studies have so far been made in 9 of the survivors Intravitam fixation by Wittmaack s method was performed at varying periods after irradiation and the temporal bones were sent to Dr C S Hallpike at the Medical Research Council Otological Unit to whom we are deeply indebted for the decalcification preparation and staining of serial celloidin sections and helpful comment on them

Sections were then shown from an animal killed 8 days after irradiation at 1 megacycle/sec The cristae of the semicircular canals and the utricular and saccular maculae showed dilated blood vessels disorganisation of the neuro epithelium and absence of the cuticular membrane changes cor



Fig. 1

responding very closely with those found by Lumsden and his co-workers in the cat.

The basal turn of the cochlea showed gross damage at the basal end, less severe damage in the middle reaches and surprisingly, severe damage and haemorrhage at the apex (Fig. 1).

Sections of the animals killed three months after irradiation at 1 megacycle sec showed persisting changes in the utricular and saccular maculae,



Fig. 2

and to a lesser extent in the ampullary cristae while the cochlear changes were almost negligible

The findings after irradiation at 3 and 5 megacycles/sec were *clinically* identical and histologically similar but an interesting feature associated with these higher frequencies was the appearance of a network of fibroblasts in the region of the point of application of the ultra sound This is well *shown* in the perilymphatic space of the lateral canal (Fig 2)

It is interesting to note that histological cochlear damage in the sheep is frequently heavy in the basal and apical portions We have *sometimes* observed in the human that after treatment the hearing at the highest and lowest frequencies is made worse while it remains unaltered or sometimes improves in the middle of the frequency range

We speculate that the peculiar configuration of the cochlea happens to concentrate the energy of the internally reflected ultra sound in the basal and apical turns leaving a less heavily affected middle region

In conclusion we find that although on the whole the histological effects achieved are more marked in the vestibular system than in the cochlea the difference is not great and as there are fairly wide individual variations in vulnerability treatment with this potent and valuable agent must always carry some risk of cochlear damage especially in dealing with a human labyrinth which is already the seat of a degenerative process

fications introduced by Mr Angell James and Dr Freundlich Failure means underdosage and I now put forward for discussion three reasons for this

One minor cause of underdosage was that in the early cases we did not bevel the bone over the lateral semicircular canal down to the blue line I think it is essential to do this as by this means we know that the bone has been reduced to less than a millimetre in thickness Personally I use a flat hand chisel for this rather than a drill as I think that this provides an automatic flat surface for good contact with the Transducer Head

A second cause of underdosage is in my opinion that until comparatively recently we were content to accept paralytic nystagmus as an end point without waiting to see whether irritative nystagmus recurred and then reapplying the ultrasound until the paralytic nystagmus was permanent Admittedly we went on for 10 minutes after paralytic nystagmus had been obtained but if the emission of ultrasound was irregular or not up to full strength this still constituted underdosage which is a partial failure of equipment not appreciated by the operator at the time

For this method to be effective it is essential that the output is absolutely steady and up to strength I am sure that at times our equipment while not failing completely had unknown to the operator at the time not been working at full efficiency This produced slow reactions and indefinite end points and this potential fault can only be overcome by an efficient monitoring system It follows therefore that if the method is to be used it is essential to have available the services of a competent physicist trained and interested in the subject Originally we did not have one available at the London Hospital but thanks to the interest of Dr I A W Kemp and Mr D O Bottrell of the Department of Physics we now have that assistance and this has made a great improvement in the efficiency of the apparatus I would now go so far as to say that I do not consider it justifiable to use this method unless a physicist is available to supervise the equipment

I have chosen to discuss failures rather than successes but in closing I want to make it quite clear that I am convinced that ultrasound is at the moment the best method we have in dealing with the case of aural vertigo which defies conservative treatment

ULTRASOUND IN THE TREATMENT OF MENIERE'S DISEASE

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We have been using ultrasonic surgery for treatment of Meniere's disease for over six years. Our experience now covers 200 patients. This type of surgery has been giving a rather gratifying result. The patients in our series have been suffering from Meniere's disease from 2–15 years or longer. All of them have had the benefit of conservative therapy, most of them have tried all known types of medical therapy. Most of the patients have been unable to perform their usual daily duties for long periods of time.

Symptoms of labyrinthine hydrops occurred in both ears in over 25% of the patients. The lapse of time between occurrence of symptoms in the two ears varied from a few months to ten years. Fluctuation of hearing continued in a high percentage of the patients for as long as 4–8 years. In a sizeable proportion of the patients who had fluctuating hearing, discrimination improved with improvement of the pure tone thresholds. These last two findings have heavily influenced me to avoid destructive labyrinthine surgery with very few exceptions.

Good post-operative results were closely related to destruction of vestibular activity as proven by ice water stimulation. 85% of the patients resumed normal activities after the first operation. An additional 5% resumed normal activity after a second irradiation with ultrasound.

The hearing decreased following ultrasonic surgery in approximately 8% of the patients, some of them with complete loss of hearing. We have not been impressed by any benefit in regard to improvement of hearing following ultrasonic surgery. If there was any fluctuation of hearing occurring before surgery the same fluctuation in many cases continued post-operatively.

Facial paralysis, immediate or delayed, occurred in 6% of the patients. All of these recovered but in three cases the return of function took over eight months. Operative facial paralysis is usually explained by (1) direct effect of heat transmitted from the tip of the applicator to the labyrinth and facial nerve, (2) by transformation of ultrasound into excessive heat in the bone, (3) by faulty positioning of the applicator, causing direct irradiation of the horizontal portion of the facial nerve. This risk is certainly higher with increase of ultrasonic energy applied. In one instance facial paralysis occurred after application of ultrasound for only 30 seconds. The applicator was found to be no warmer than body temperature in this instance and the

This study was supported by Grant NB 3854, U.S. Department of Health, Education and Welfare.





Fig. 1 Fig. 2

Fig. 1. 0.1 mm bone separates lumen (L) of lateral semicircular canal from horizontal portion of facial nerve (F). Vertical section.

Fig. 2. 0.1 mm bone separates lumen (L) of lateral semicircular canal from horizontal portion of facial nerve (F). Vertical section.

tip of the applicator was placed on the safest area, namely the posterior portion of the lateral semicircular canal. As long as the incus is in place faulty positioning of the applicator is not likely to occur. Facial paralysis has occurred with or without cooling the operating field with saline solution.

As mentioned above, facial paralysis occurred after only 30 seconds irradiation in one case. This experience raises the question of the possibility of other factors playing a role in producing facial paralysis during ultrasonic surgery. Anatomical variations were investigated in serial sections of 100 temporal bones, most of them in vertical sections. The thinnest portion of the bone separating the ampulla of the lateral semicircular canal from the horizontal facial nerve was measured under the microscope. The thickness of bone separating the lumen of the ampullated end of the lateral semicircular canal and the facial nerve varied from 0.1 to 0.6 mm. In 17 % of the bones this thickness did not exceed 0.15 mm. It is obvious that ultrasonic energy has to destroy the crista of the lateral semicircular canal in order to obtain good control of the disease. It is just as obvious that once ultrasonic energy has reached the crista it may have to traverse only 0.1 mm of bone in order to reach the facial nerve. The attenuation of energy rapidly decreases with decrease of the diameter of the bone. The patients whose facial nerve is



Fig 3 Intratympanic portion of facial nerve (F) crosses labyrinth in a diagonal course—going from knee of the nerve to roof of attic Vertical section

better protected due to anatomical variations run a very small or no risk It is logical that the least possible energy should be used because we cannot possibly know in an individual case when we will encounter a very thin separating bony partition between the semi circular canal and the facial nerve A thin bony lamella of 0 1 mm hardly absorbs any energy and this energy would pass unhindered from the labyrinth to the facial nerve An occasional facial paralysis following ultrasonic surgery is probably unavoidable in my opinion (Figs 1 and 2)

The distance between the surgical dome of the lateral semi circular canal to the facial nerve equally shows wide anatomical variations but it represents a safe distance using our usual technique

The thickness of the labyrinthine capsule varies between 0 2 to 0 8 mm Depending on the thickness of the labyrinthine capsule and on the amount of bone removed with the drill more or less energy will reach the labyrinth and the facial nerve

There was one temporal bone in which the facial nerve ran an almost vertical course in its second portion Coming from the knee it crossed the lateral semi circular canal in a diagonal direction and left the tympanic cavity through the roof of the attic One could hardly be prepared for such an anatomical variation even with the use of all surgical precautions However, such a variation was found only once out of 100 temporal bones It may, however, occur more frequently (Fig 3)

In conclusion I may briefly mention that we used a new ultrasonic generator and applicator designed by Mr George Kossoff of Sydney Australia. In ten patients The output has been consistently reliable and on the whole we were satisfied with this apparatus to a degree that we stopped using the [illegible] dericei instrument

Concerning Meniere's disease most interest has so far been devoted to the neuroepithelium and the walls of the membranous labyrinth while the function of the secretory epithelium has been rather neglected. The fact that complete relief from vertigo can be obtained with ultrasound without a complete elimination of the caloric response to 30°C and 44°C water has drawn our attention to the role of the secretory epithelium.

METHODS

After decapitation the temporal part of the pigeon's cranium was excised immediately fixed in 6 % formalin for 48 hours and after rinsing in running water decalcified in 5 % hydrochloroacetic acid for 5–7 days. The specimens were then vacuum embedded in paraffin.

Staining was carried out according to McManus & Mowry (1960) with

1. 0.01 % aqueous toluidine blue
2. the periodic acid Schiff (PAS) reaction
3. the Alcian blue method

RESULTS

1. In non irradiated pigeons toluidine blue staining revealed the abundant presence of a metachromatic substance which turns a red lilac colour. (Non metachromatic tissue stains blue. See Fig. 1.) This occurred in the cupulae and the otolith membranes intracellularly in the planum semilunatum and above this region forming a thin porous connected coating sometimes extending all the way upwards into the cupula. Cells on both slopes of the crest were richly supplied with metachromatic matter. The reaction to staining tells us that this substance contains acidic groups of high molecular weight material.

2. The metachromatic substance mentioned above is PAS positive which implies that it is a polysaccharide (Fig. 1 upper row right).

3. When treated with Alcian blue it turns a clear blue green colour indicating acid mucopolysaccharides (Fig. 1 upper centre and middle row).

In the lagena the knot like secretory epithelium on Reissner's membrane (corresponding to the vascular stria in mammals) produces only a very slight secretion of mucopolysaccharides compared to the epithelium in the labyrinth and the vestibule.

The present histochemical investigation confirms Dohlman's results but shows in addition that acid mucopolysaccharides are excreted from the transitional epithelium on both slopes of the crest. Our observation of a connected layer of metachromatic substance from the planum semilunatum up onto the slopes of the crest and extending all the way into the cupula may indicate that the latter is continuously supplied with mucopolysaccharides from the secretory epithelium in these regions. Similar observations were made concerning the membranes in the utricle and the saccule.



G 1 Lab rinth of normal and irradiated pigeons stained with toluid ne blue Alci [illegible] PAS [illegible] ow—lateral crest planum semilunatum and part of the utricle in a non irra liate l pigeo [illegible] to- uidine blue (left) Alcian blue (centre) and PAS (ri ht All three stains reveal [illegible] of [illegible] olysaccharides

Middle row—cross shaped crest of the anterior vertical canal and planu n sen ilunatum (l ft) utricle (right). Al ian blue

Lower row—lateral crest planum semilu [illegible] part of the utricle [illegible] irra liated pigeons stain toluid ne blue (left and centre) and PAS [illegible] nced degeneration a l atrophy of the ep well as almost complete absence of mucopol [illegible] rradiation time 20 minutes Total outpu



FIG 2 Bony labyrinth of a non irradiated pigeon after intravital staining with oxytetracycline Longitudinal section through the lateral canal and cross section through the posterior vertical canal Faint fluorescence (white patches) mainly concentrated to the surfaces of the bone

fluorescence could be observed either in treated or untreated animals The fluorescence seemed to be strongest where the tip of the transducer had been applied and diminished with increasing distance from this point In the innermost parts of the temporal bone nearest the brain only a little fluorescence was seen None has been observed in the brain itself or the meninges

The strong fluorescence in the bone walls of the labyrinth confirms our previous observation that vigorous formation of new bone takes place a few weeks after the ultrasonic irradiation Apparently the intense local heat absorption causes a lesion in the bone During the healing process new bone is formed Essentially the same changes have previously been noted in pigeons after local heating of the labyrinthine wall with glowing metal wire (Herberts Rydmark & Stahle 1954)

COMMENTS

There is reason to suppose that similar processes can take place in the human labyrinth The ability to form new bone is proved by the fact that during the early fenestration era the opening often closed spontaneously There is no doubt that bone damage resulting from ultrasound irradiation can occur in Meniere patients Altmann (1962) has observed macroscopic necrosis in the bony wall in the area of previous irradiation in some cases where the first irradiation was not successful and a second was required



FIG 3 Bony labyrinth of a pigeon three weeks after ultrasonic irradiation Intravital staining with oxytetracycline Widespread strong fluorescence in the thickened bony walls indicating lively formation of new bone The semicircular canals severely constricted in consequence

In Uppsala, too we have had numerous cases where towards the end of irradiation the yellowish and slightly transparent enchondral bone turned whiter and more opaque at the site of irradiation This probably indicates grave local bone damage It seems justified to suppose that this heals fresh bone being formed at the site If this process implies that the perilymphatic space is filled with new bone and connective tissue as is the case in the experimental animals the part of the labyrinth within the irradiated area is most probably obliterated

SUMMARY

1 The secretory epithelium in the labyrinth has been studied by means of different histochemical staining methods in normal pigeons and pigeons irradiated with ultrasound

2 An abundance of acid mucopolysaccharides is demonstrated in normal animals in the ampullae and the otolith organs

3 Acid mucopolysaccharides occur in the transitional epithelium on both slopes of the crests and may form a continuous layer covering the surface all the way up into the cupula

4 Ultrasonic irradiation can decrease the occurrence of acid mucopolysaccharides

5 The effect of ultrasound on the bony walls of the labyrinth has been studied by means of labelling with tetracycline

6 Ultrasonic irradiation leads to vigorous local bone formation, which tends to obliterate the part of the labyrinth inside the irradiated area

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THE BIOCHEMISTRY OF THE INNER EAR AND THE CONSEQUENCES OF TREATMENT BY ULTRASOUND

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Studies on the biochemistry of the inner ear were begun in our unit at the farsighted suggestion of Dr C S Hallpike F R S In the first place they were concerned with the analysis of the fluids More recently we have studied the metabolism of the inner ear tissues and changes in fluid composition produced by a variety of conditions The work I am going to describe was carried out in collaboration with Dr K Rodgers Dr D Exley and ourselves

To a biochemist the dominant feature of the inner ear is the disequilibrium between Na^+ and K^+ in the perilymph and endolymph (Table 1) Perilymph has the usual composition of any extracellular fluid whereas endolymph like saliva resembles intracellular fluid (1 2) There is considerable indirect evidence that the function of the inner ear end organs depends on the maintenance of the composition of the fluids For instance anoxia or changes in fluid composition cause changes in or loss of various potentials (3 4) Meniere s disease which is accompanied by a hydrops of the endolymphatic space is one pathological condition associated with a change in fluid composition (5)

I wish to discuss first some ideas on the origin of the fluids and their rate of formation and circulation

The origin of perilymph has been studied by injecting isotopic phosphate ($KH_2P^{32}O_4$) and C^{14}
pigs (6) Both isotop
in the scala tympan
the sub arachnoid space into the cochlea was greatly affected by the position and movements of the head Flow from the cochlea into the C S F was negligible under the normal conditions P^{32} did not appear in the utricular endolymph until 1½–2 hrs after injection into the C S F and which by then was almost completely equilibrated with the blood C^{14} did not appear in the endolymph in periods up to 5–6 hrs after injection These results support the idea long held that the perilymphatic space is a diverticulum of the arachnoid space and is filled with C S F which can flow freely through the cochlear aqueduct (7) Reissner s membrane would appear to be relatively impermeable to phosphate These experiments have the advantage that until the actual collection of the fluids there has been a minimum of interference with the inner ear They have served as a pattern for experiments now in progress on the flow of ions between perilymph and endolymph This would

TABLE 1 *Analysis of inner ear fluids of the guinea pig (after Citron et al (1) and Rodgers (2))*

Constituent	Cerebrospinal fluid	Perilymph	Utricular endolymph
Sodium (meq/l)	150.0	130–160	50–26.0
Potassium	3.0–5.0	~5.0	~142.0
Calcium (meq/l)	3.0	3.0	2.9
Magnesium (meq/l)	2.0	2.0	0.9
Phosphate (m moles/l)	0.63	0.48	0.46
Chloride (meq/l)	122.0	120.0	110.0
Protein (meq/100 ml)	20.0	75.0	25.0
Non protein nitrogen (mg/100 ml)	21.0	20.0	21.5
Total carbohydrate as glucose (mg/100 ml)	110.0	140.0	135.0
Hexosamine (mg/100 ml)	—	6.5	6.5

appear to be very dependent on the maintenance of metabolism of the inner ear tissues, especially Reissner's membrane. Thus, we have found that perilymph and endolymph mix rapidly after death. Complete equilibration takes 1½ to two hours but already some mixing is detectable 10 min after death (2) (Fig 1).

It would be expected that the formation and maintenance of the ionic disequilibrium between endolymph and perilymph could be maintained only by the expenditure of energy in the form of adenosine triphosphate (ATP) produced by a tissue or tissues lining the various scala. This is supported by the rapid changes which occur after death or anoxia. We have therefore measured the respiration of the inner ear tissues and the results are shown in Table 2 (8). The stria vascularis was found to have a very high rate of respiration, indeed this tissue respires more rapidly than any other mammalian tissue so far studied. Reissner's membrane too was unexpectedly found to respire rapidly. Examination by light and electron microscopy indicated that the tissues were still intact after the measurements, this especially applied to the mitochondria (8).

On the basis of these results we have estimated the approximate rate of turnover of endolymph on the assumption that the stria vascularis transports Na^+ during the secretory process. The other main assumptions are that the P/O ratio is 3 and that the O_2/Na ratio is twelve (for a discussion of this latter point see Leaf (9) and Whittam (10)). We have estimated the volume of endolymph as 5 µl of the volume of the stria and vascularis as 1–0.5 µl. On these assumptions the turnover of endolymph is once in every 3½–6 min. This is a rapid rate but previous work on changes in potential when endolymph secretion is interferred with and our own work on changes after death would support this estimate. Ion transport during endolymph formation is

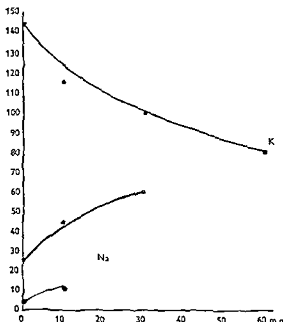


FIG 1 Changes in the Na^+ and K^+ concentration of utricular endolymph and perilymph after death Guinea pigs were killed by opening the thorax under nembutal anaesthesia and severing the carotid arteries

likely to demand at least 40 % of the available energy supplies and to maintain the rapid turnover of endolymph (8) means that the process is very sensitive to oxygen supply The ultra structure of the stria vascularis (Fig 2) also lends further support of its involvement in the secretory process (8)

It is significant in this respect that rate of respiration of the stria vascularis

TABLE 2 *The respiration of inner ear and other tissues of the guinea pig*

The tissues were separated from guinea pigs under nembutal anaesthesia and their respiration measured by means of Cartesian divers (8)

Respiration rate of tissues lining the membranous labyrinth of the guinea pig compared with that of other tissues

Tissue	Respiration rate µl O_2/µl fixed tissue/hour
Stria vascularis	10 1
Spiral ligament	0 8
Organ of Corti	0 9
Reissner s membrane	7 8
Choroid plexus	5 C
Kidney proximal and distal tubules	3
Kidney collecting tubules	(8



Fig. 2. Electron micrograph of the stria vascularis of a normal mouse. The tissue was separated and fixed in buffered osmic acid, embedded in araldite and sections cut in a Huxley microtome.

of Shaker 1 mice decreases compared with their normal litter mates as the waltzing syndrome develops (Table 3).

We would like now to consider two hypothetical schemes for inner ear fluid secretion and maintenance. The first (Fig. 3A) is based on that of Naftalin & Harrison (11). Here perilymph is regarded as a secretion or

Table 3. *Changes in the respiration of the stria vascularis from normal and Shaker 1 mice*

Shaker 1 and normal mice were r d an l the str a va cular s separated a l stud ed as before (8, 2).

Resp t o rate of the stria va cular s of the normal mouse an l the Shal er 1 n ouse

Mous	Age (days) 18 20	30	0	100
No n al	1? 6	17 6	17 6	12 8
Shak r 1	17 9	12 6	6 1	7

R p at on rate $\mu l\ O_2$ l f xed t ssue hour

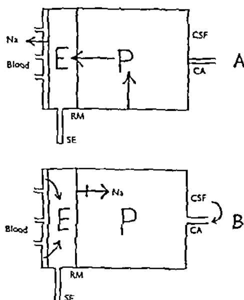


Fig 3 Schemes of the possible route of inner ear fluid secretion maintenance *E* and *P* indicate the perilymph and endolymph respectively *CSF* and *CA* the cerebrospinal fluid and cochlear aqueduct *RM* Reissners membrane and *SE* saccus endolymphaticus

exudate from the perilymphatic spaces and not as C S F This is based mainly on the increased protein content in perilymph found by Exley (1) Perilymph is then considered to flow freely across Reissner s membrane into the scala media *where it is changed by the stria vascularis in a manner similar to that* which occurs in the kidney tubule during the formation of urine That is, Na^+ and water are actively transported into the blood while K^+ is concen trated We consider that the free passage of perilymph across Reissners membrane *is unlikely in view of the foregoing results* and consider that this membrane is not freely permeable to Na^+ This is indicated in 2 B, where endolymph is shown to be secreted by tissues lining the scala media a pro cess analogous to the formation and secretion of saliva This scheme would also demand a separate adsorption process which in the absence of contrary evidence we would assign to the saccus endolymphaticus (12) This ad sorption process could either be passive or active and we are attempting to isolate the saccus and study the metabolism of the tissue components

At this stage we have the following picture on which our present experi ments are based The perilymph is replaced at a slow rate with C S F by flow through the cochlear aqueduct In contrast the endolymph is turned over at a rapid rate by secretion and adsorption processes which occur in tissues lining the endolymphatic system We would suggest that the vas cular tissues lining the endolymphatic spaces are responsible for secreting endolymph while Reissners membrane maintains the disequilibrium between the fluids by its impermeability

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MYRINGOPLASTY

Four years' experience of temporal fascia grafts

BY

URBAN ÖRTEGREN, M L

ACTA OTO LARYNGOLOGICA KARLAVAGEN 41, STOCKHOLM O

ACTA OTO-LARYNGOLOGICA
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MYRINGOPLASTY

Four years' experience of temporal fascia grafts

by
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LUND 1964

CONTENTS

INTRODUCTION

Chronic otitis has 2 components inflammation and hearing loss During the first 4 decades of the 20th century therapy aimed at either of these It consisted of radical cure with prophylactic removal of osteitic or inflammatory tissue to avoid complications, or prothetic treatment of the perforation of the drum in cases where actual inflammatory changes could not be observed The operative cure often involved the removal of structures in the middle ear important for normal hearing

A radical change in the post-operative prognosis of chronic otitis has been the result of the pioneer works of Wullstein and Zöllner on the operative cure of chronic otitis by means of tympanoplasty The improvement was that instead *of removing decayed parts of the middle ear important for normal hearing*, these parts were built up by means of various plastic surgical procedures

For 5 or 6 years there has been a desire in many places of the world to improve the results of these pioneers This desire has led to many modifications of the old methods or to the development of quite new ones In our department too, there was early a wish to improve the results obtained by the earlier methods At an early stage it was obvious that highly increased manual ability in the performance of the plastic repair of the defects of the middle ear was not enough, but that a good post operative result is the outcome of a good many factors The group started by studying the importance of the quality of the transplant Soon, however, it became quite obvious that the function of the *Eustachian tube plays a central part This has been pointed out* by most authors on this subject It was, however, suspected that earlier methods for measuring the function of the tube were not sufficiently exact For this reason exact, objective methods for measuring the function of the tube have been worked out parallel with the transplantation studies Further work in this field is in progress At estimation of the prognosis of reparative middle ear surgery, there is an intimate connection between the importance of the tubal function and that of the cellularity Consequently an exact, volumetric method has been developed for clinical measuring of the cellularity of the mastoid combined with studies of the tubal function

Since the mid-1940's allergic manifestations in the middle ear have been studied at the clinic (Koch, 1947) In this connection, it is therefore natural to discuss the problem whether bacterial allergy is of any importance for post operative tympanoplastic results Studies in the field are therefore in progress

The present paper deals with the results of transplantation studies carried out since 1957 In order to obtain uniform conditions in the study we only deal with myringoplasty, i e repair of drum perforations in cases with intact ossicular chain (tympanoplasty of type I according to Wullstein)

History

Covering of drum perforations has been performed for 300 years However, the methods used have changed from time to time and can be divided into 3 main types

I Prothetic covering, characterized by covering with artificial material
II Skin transplantation, in which different types of skin were mainly used for covering
III Connective tissue transplantation, in which use is increasingly made of the graft which is richest in connective tissue

Prothetic covering

In a treatise Marcus Banzer (1640) described a method for covering drum perforations with a piece of pig's bladder Autenrieth (1815) instead used the wall of fish's air bladder impregnated with varnish as prothetic material In some cases good hearing results were primarily reported by this treatment Yearsley (1848) replaced these prothetic materials with a membrane of cotton wool soaked in heavy oil Toynbee (1852) used a more advanced technique with a thin rubber membrane which could be applied and removed by the patient himself by means of a thin silver thread attached to its center Modifications of this method were later described by Lucae and Politzer (1908) Katz (1889) used a thin membrane of celloidin as a cover, while Nadoleczny found protheses of silver leaf less irritating to the tissues of the middle ear A method for obtaining thinner prothetic material was described by Dohlman (1923), who made a thin membrane of uniform thickness by making a drop of zapon-varnish spread on a water level and dry Isaacs (1925) instead used collodium since he was convinced that complete transparency of the membrane was very important Several times (1928, 1930, 1934, 1938) Nasiell described different phases of development of protheses made of cellophane foil and fixed to the drum by ointment Hall (1951) described covering of drum perforations with rice paper fixed and impregnated with plastic glue This treatment was often preceded by cautery of the rims of the perforation and in this way healing of the perforation during prothetic treatment was sometimes obtained

Comment

Methods for covering perforations during this period aimed at palliative hearing improvement, often at the cost of a running middle ear, healing of the perforation sometimes occurred but was not intended At the end of the 19th centr[illegible] dry middle ear was considered to preclude prothetic treatment of drum pe[illegible]ration since the danger of causing a moist middle ear was too great [illegible] however, aimed systematically not only at palliative hearing imp[illegible] [illegible]al healing

Skin transplantat

During the period of prothetic covering the dru temporarily to improve the patient's hearing The the perforation can be ascribed to Politzer (1885, for closing the perforation by means of scars obt and growing inwards from the rims Earlier Bertold (18 cover drum perforations with thin thiersch like skin f were obtained by stripping with adhesive tape. Extrem adhered to the tape when stripped off, and were then drum The method was not commonly used when desc adopted by Schulhoff and Valdez (1944)

Wullstein (1952) published a method for split skin of the drum by tympanoplastic operations in cases o was a direct result of the intense research in this f at the beginning of the 1950's Soon followed Z also described split skin transplantation for cov Zollner introduced tympanoplasties intended to combined with defects of the ossicles He pointed mally functioning Eustachian tube His descrip works were soon developed in other papers Ho in which the split skin graft of the German m ness skin grafts Wullstein and Zollner devel different lines Wullstein (1953) said that he cause of its low resistance, preferring full t since skin of this site is thin and hairless A described, there is, however, no division into Without giving the time of observation W attained post operative hearing = pre operat Furthermore, there was a dry middle ear described 21 myringoplasties performed failures In 1955 Wullstein gave a system rations which has ever since been followed account of 89 cases of myringoplasty It dB line while still 52 % more reached th were used as grafts Wright (1956) ga formed with different types of skin graf by grafting was pointed out and th was emphazised In 34 cases grafted w were 25 "takes" and 9 failures and 25 mastoid area showed 22 "takes" and with full thickness skin ther was only "pedicle flaps from the ear can , 4 fail

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In a paper dealing with 400 tympanoplasties Wullstein (1956) discussed the inspection of the middle ear during operation The following steps ought to be taken 1. Control of the antrum 2 Upper control of the middle ear 3 Lower control of the middle ear In 1 it is necessary to "enlarge the bony auditory meatus a little bit backward and then open the antrum through a drill hole only closely behind a broad bridge which gives protection to the whole epitympanum and the ossicles" 2 is done by mobilization of the drum and limbus, whereby the epitympanum can be inspected, and 3 is done by detaching the drum and limbus so far backward-downward that the hypotympanum can be inspected These are clear and distinct statements There were 103 myringoplasties in the series in which post operative hearing results were given 32 % reached the 15 dB line and 51 % more the 30 dB line In all cases full thickness skin grafts were used Zollner (1957) described his making "Verschlussplastik und Meat-Antrotomi" in the same situation Split skin grafts 0,5—0,6 mm thick were used There were 52 such cases with post-operative results There were 43 "takes' or 83 %, while the hearing results immediately post operatively were given rather as hearing improvement or as persisting hearing loss Forty seven out of 52 cases had a hearing improvement of 10—40 dB, 49 or 94 % reached the 30 dB-line, and 32, i e 62 % the 15 dB line

Wullstein (1957) reported a series of tympanoplasties of 1000 cases, of which 23 % were myringoplasties Post operative hearing results were given as bone air gap and it was shown that in the first half of the series 34 % of the cases had a bone-air gap of 0—15 dB, while in the second part this result was reached in 70 % The number of cases in group 2 was not given Full-thickness retro auricular skin was used as grafts and to support the graft "the tympanic cavity has been filled with reabsorbable substance"

Guilford, Wright, Draper (1959) have published results of tympanoplasties performed with thick split skin grafts The series contained 154 tympanoplasties of all categories which have not been divided into different types They carefully discussed different types and thickness of skin grafts and found thick split skin preferable because of the structure of the vascularization of the skin The importance of atraumatic grafting was emphazised, so was the danger of infection of the vascular bed and the importance of fixing the graft with the lowest possible pressure of the packing There were 97 takes and 57 failures Takes were observed for 3—48 months, while the follow-up of the failures covered 1—8 months The authors also emphasized the necessity of a good tubal function for good results The examination has been carried out by politzeration and calibrated Valsalva test

Brandow (1960) reached the same conclusion and had nearly the same preoperative operative, and post operative routine except that he used retroauricular full thickness skin grafts There were 28 myringoplasties in the series and 21 were reported as "serviceable hearing" There were 9 failures

[illegible] 60) has given long-term results of a study of the Wullstein ma[illegible] [illegible]panoplasties The series contained 322 myringoplasties of

type I, only 80 of these were re-examined 1—2 and 36 months after operation. Among these 80 cases there were 70 % with a middle ear component of < 15 dB and 96 % < 30 dB 1—2 months post-operatively, while the same percentage 36 months post operatively were 66 resp. 89. Ninety-two per cent of the drums were well movable post-operatively but the number of perforations was not given.

Agazzi (1960) presented long term results of a series of 292 tympanoplasties performed between 1955 and 1958, all of the cases were re-examined at least 1 year after operation. The material contained 94 myringoplasties, which were mostly performed with skin grafts. However, a certain number, which has not been stated, were performed with periostium. Hearing results were provided in the groups "improved", "unimproved", and "worse". Hearing was improved in 48,8 % and there were 18 % perforations, but also 32,9 % moist middle ears post-operatively. Beales (1961), Booth (1961) and Proctor (1962) have published results on tympanoplasties performed with full thickness grafts, and with post operative healing and hearing results which agree with those earlier related. Frenckner (1955) gave a method for myringoplasties covering the perforation with pedicle grafts from the ear canal skin. Of the cases operated upon, 15 were re-examined post-operatively with only 1 failure. Sooy (1961) presented a comparison between different grafting methods, full-thickness skin, graft from the ear canal skin, pedicle graft from the ear canal skin and different types of vein grafts. Skin grafts showed 12 takes out of 25 cases, pedicle grafts 11 takes out of 16 cases.

TABLE I

\	Year	Tubal function *pre op*	Graft	Number of cases	Time of obs. months	% or number "takes	% bone air gap 0—10 dB	% hearing loss 0—15 dB	% hearing loss 16—30 dB	Cause of failure discussed
M	1640		Pgs bladder							
Au nrieth	1815		Fish s air bladder							
Yearsley	1848		Cotton wool							
Toynbee	1852		Rubber							
Berthold	1878		Skin							
Politzer A	1885 1885		Caut Rubber							
Schulhoff Waldez	1944		Skin							
Hall A	1951		Rice paper	*146 infl* *30 traumat*		33 cases 29 cases				×
House	1953		Skin full thick							
Schr mpf	1954		Amnion	53		48 cases				
Frenckner	1955		Pedicle graft	15		14 cases				
Zollner	1955	Good	Split	21		15 cases				
Wullstein	1955		Skin full thick	89				32		

TABLE I

Authors	Year	Tubal *function* pre op	Graft	Number of cases	Time of obs *months*	% or number '*takes*'	% bone-air gap *0—10 dB*	% hearing loss *0—10 dB*	% hearing loss *16—30 dB*	Cause of failure discussed
Wright	1956		1 Split	34		25 cases				×
			2 Split	23		22 cases				
			3 Skin *full thick*	4		1 cases				
			4 Pedicle	4		0 cases				
Wullstein	1956	Good	*Skin* full thick	103				32	51	×
Zollner	1957	Good	Split	52		83 %		62	32	×
Wullstein	1957		Skin full thick	57				62		
Beales	1958		Skin full thick							
Wullstein	1958	Good	Skin full thick	?/500 ?/500			11 45	23 25	49 26	×
Guilford	*1959*		*Split*	154	3—48	97 cases				×
Ortegren	1959	Good	Fascia	5	3	5 cases	5			
Garcia Ibanez	1959		*Skin* full thick	27		*14 cases*		14 cases		
[illegible]	1960		Split							
[illegible]	1960		Skin full thick							
[illegible]	[illegible]		Skin	4						
Brandow	1960		Skin *full thick*	28		3 cases			75	×

TABLE I

r	Year	Tubal *function* pre op	Graft	Number *of* cases	Time of obs months	% or number *takes	% bone air gap 0—10 dB	% hearing loss 0—15 dB	% hearing loss 16—30 dB	Cause of failure discussed
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TABLE I

Authors	Year	Tubal function pre op	Graft	Number of cases	Time of obs months	% or numbers "takes"	% bone-air gap 0—10 dB	% hearing loss 0—15 dB	% hearing loss 16—30 dB	Cause of failure discussed
Willems	1962		Mucous membr							
Heermann	1962		Fascia	55	18	50 cases				
Tabb	1963		Vein	138						
Kley	1963		Fascia							
Nickel	1963	Good	Homog vein	34		28 cases				
Portmann M	1963	Good	Skin vein conn tiss	39/50 op		84 %			62	
Austin	1963		Vein	117/190 op	12	82 %	70	19	-	/

Comment

After 1950, palliative treatment of chronic otitis has been abandoned in favour of a therapy aiming at definite healing This involves the use of skin in different shapes and from different sites for tympanoplastic surgery Nevertheless, *there is no completely thorough, reliable report of long-term results* that could be used as a basis for estimating the clinical possibilities and value of the methods (table I) Thus, there are no standard rules for presenting the material, so the results of one author can only with great difficulty be compared with those of another Some authors only account for the healing results, omitting the hearing, whereas others only discuss the hearing results without mentioning the healing factors In this group of authors there is not even any agreement on how to give the best and easiest survey of the hearing results pre and post-operatively Mention is made of units like bone-air gap, post-operative hearing improvement, remaining hearing loss, social hearing attained or not, and in one case also of post operative hearing better or worse than the pre operative hearing state with a good hearing aid As a rule, time of observation post operatively is not given at all and, if it is, only part of the series re-examined is mostly given, and without any information on the basis on which the selection is made In accounts of the causes of failures, post-operative re infection is the commonest in spite of treatment with antibiotics, even locally applied, but there are cases with "no apparent cause" of perforation and late failures, Wright (1956) These last 2 groups have been studied by among others Beickert (1958) and Kley (1959) It is shown that post-operative perforations may occur owing to sweat- and sebaceous glands and hair follicles in the grafted skin In the case of split-skin grafts, it happens that a "Lappen-cholesteatoma" develops or microscopical perforations appear when glands and hair are severed by grafting, or retention cysts develop from the same parts of full-thickness grafts Another difficulty, also emphasized, is that of effecting a complete adaptation to the vascular bed the elastic fibres of the skin cause the graft to roll and curl, thereby leaving a space between the graft and its bed, which prevents nutrition

Connective tissue transplantation

It appears from the above account that myringoplasty with skin grafts in the 1950's has not been satisfactory It is thus not surprising that there is some doubt as to whether the results are good enough This is probably the reason why other grafts besides skin have been tried so extensively for the last 4 years

The author (1959) gave a preliminary report on a comparison between results with fascial grafts and a similar series of skin grafts used as controls in myringoplasty Out of 5 myringoplasties performed with fascia from m temporalis there were 5 takes 3 months after operation, and during the same period [illegible] failures out of 7 skin grafted myringoplasties H Heermann (1960)

made a thorough description of a method for fascial grafting used by him for 2 years Shea (1960) described a method for closing central perforations of the drum by means of a vein graft The graft was placed on the inner side of the drum with the intima side inwards Tabb (1960) described a similar method independently of Shea Forman (1960) showed how homogeneous corneal grafts can be used for myringoplasty

Livingstone and Miller (1961) described 26 myringoplasties with vein graft re examined 6 months post-operatively There were 70 % takes, and 73 % of the cases had reached the 30 dB-line Storrs (1961) recorded 6 fascial grafted myringoplasties re-examined 1—5 months after treatment with 6 takes Schlosser and Pratt (1961) obtained 2 takes out of 3 cases with the same technique

Heermann, J (1962) operated on, and 18 months later re examined, 55 myringoplasties with fascial grafts Among these there were 50 takes In a series of 503 tympanoplasties Austin (1963) performed 190 myringoplasties with vein-grafts One hundred and seventeen were re examined 12 months later There were 14 failures and in 89 % of the cases there was a bone air gap of 0—20 dB

Comment

It is remarkable that in a few years there has been much more accurate information on the results of different forms of connective tissue grafting than on the results of skin grafting As far as healing is concerned, the results seem to be much better in spite of smaller series

J Heermann (1962) has stated the reason for his attitude to connective tissue graft in fascial form in the following way "Bei der freitransplantierten retroaurikularen Haut fanden wir folgende Nachteile Neigung zu starker Desqamation, rezidivierender allergischer Sekretion, Lappencholesteatombildung " These points of view were stated by the author in 1959 In his paper it was also pointed out that the construction of fascial grafts is less differentiated, so these ought to adapt themselves more easily in a new surrounding Fascial

vascular bed The relatively limited number of cells results in lower metabolism and thereby in stronger resistance to poor healing conditions Since further connective tissue surface becomes epithelialized from the edge of the vascular bed with a velocity which reduces the diametre of the unepithelialized surface by 1 mm/day (Howes, 1943, Amiri, 1963), it is possible for the drum surface to be fully epithelialized in less than 10 days both on the in and the outside Link (1960) showed that a corium graft — a skin graft without epithelium — "takes much more easily This is explained by the fact that skin grafts give auto immunization because of the antigen component bound to the nuclear substance of the epithelial cell This might explain the allergically induced

1) healing results for fascia versus skin,
2) effects of the patient's age upon healing and hearing results, respectively,
3) effect of observation time upon healing and hearing results, respectively,
4) the importance of tubal function for post operative results,
5) the importance of cellularity of the mastoid for healing results

Present investigations

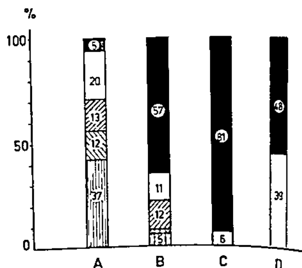
Material

The author has performed 87 myringoplasties grafted with fascia during the period from December 1957 to September 1961 The material consists only of cases of type I according to Wullstein, i e cases with drum perforation and an intact ossicle chain with good movability Perforations were central in 81 cases and marginal in 6 The genesis of the perforation was in 11 cases traumatic with inflammatory complications The age of the patients in the series is fairly evenly distributed from 0—70 years (fig 1) In the group <40 years 14 cases are found between 40 and 50 years, 13 between 50 and 60, and 10 between 60 and 70 years All cases examined by politzeration and Valsalva's manoeuvre showed air passage through the tube In 47 cases cellularity was small and in 40 normal or large, as estimated at routine examination by the X-ray Department During the period from 1958 to 1959, 20 myringoplasties have been performed with identical method and using the same principles for the selection of the cases with one exception, namely that split skin has been used for grafting (fig 2) The qualities of the skin grafted series is pre operatively much the same as those of the fascial graft material

Pre-operative examination

Great importance has been attached to anamnestic data Earlier disorders are analysed The length and etiological factors of the disorders and the different symptoms are mapped out In addition to a thorough otological examination, the pre operative physical check up includes an audiological analysis supplemented with microscopic examination of the middle ear and examination with a covering prothesis, X ray examination of the ear, allergologic examination and testing of tubal function Only passability for air at politzeration and Valsalva's manoeuvre, however, have been tested in the entire material In 1961, 11 cases were tested for tubal function with a method worked out in the clinic This method gives maximated, constant pressure in the rhino-pharynx and an objective very sensitive registration of the tubal air passage (Ingelstedt, Ortegren 19[illegible])

FIG 1



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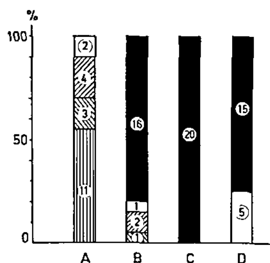
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Pre-operative account of fascia grafted series
in per cent histogram (87 cases)

Column A — age distribution
" B — etiology of the perforation
" C — character of the perforation
" D — mastoid cellularity
⊗ — number of cases in the column

	A	B	C	D
	0—10 years	chronic otitis	central perf	[illegible]
	11—20	trauma	marginal perf	[illegible]
	21—30	chron otit (scarlatina)		
	31—40	chron otit (morbilli)		
	> 41	unknown		

FIG 2



Pre operative account of skin grafted series in
per cent histogram (20 cases)

Column A — age distribution
„ B — etiology of the perforation
„ C — character of the perforation
„ D — mastoid cellularity
Ⓧ — number of cases in the column

	A	B	C	D
(black)	0—10 years	chronic otitis	central perf	small
(white)	11—20	trauma	marginal perf	normal or large
(hatched)	21—30	chron otit (*scarlatina*)		
(cross-hatched)	31—40	chron otit (morbilli)		
(vertical lines)	> 41	unknown		

Pre-operative treatment

The pre operative therapy begins by a thorough treatment in order to dry up the middle ear in cases of a running ear Infection prophylaxis is carried out and the ear is kept dry for 4 months by means of a covering prothesis according to Hall In cases where a running ear cannot be made to dry by conservative treatment, the infected middle ear should be treated by antrotomy In these cases the myringoplasty has not been carried out immediately, but only after the middle ear has healed and dried Exceptions to this rule are cases with early cholesteatoma that can be extracted in toto and where the defects of the drum and skin of the ear canal are temporarily covered to avoid relapse

Operative procedure

Anesthesia

The operative cure is performed under local anesthesia, 1 % Xylocaine ® exadrine General anesthesia is used very rarely and only if the patient is unable to cooperate Local anesthesia is preferred because the result of intratympanic treatment can be controlled by hearing tests during operation

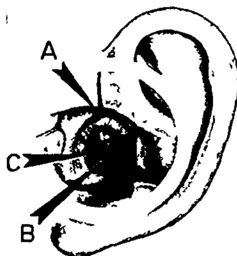


FIG 3
Illustration of operation method Incision.
Principle sketch of
A — end aural incision
B — drum perforation
C — deepithelialization area in magnification

Preparation of the vascular bed

The operation is always initiated by a thorough de epithelialization of the edges of the perforation to an extent which in all directions is equal to the diametre of the perforation This is done microscopically in a magnification to 10 times the size (Fig 3)

Inspection of the middle ear

Next an exploration is made of the tympanum through a modified Lempert-incision in order to ascertain possible defects of the ossicle chain and make sure that no cholesteatoma is present (Fig 4) The middle ear is cleared of adhesions and granulations are removed The tube is examined with a probe from the middle ear, and great care is taken to prevent lesions Cholesteatomas in this region are removed entirely The rims of the perforation are excided with a Mehmke tympanic membrane punch After the middle ear and vascular bed have been treated, adrenaline 1 % (sic) is locally applied as haemostatic in order to avoid any bleeding between graft and bed

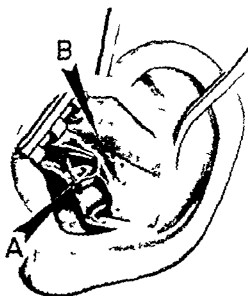


FIG 4
Illustration of operation method
Exploration of the tympanic cavity and the temporal fascia
Principle sketch of A — explored middle ear in magnification
B — m temporal s

Preparation of the graft

Not until now is a graft prepared from the temporal fascia (Fig 5) big enough to allow the graft to shrink It is important that only fascia is used in the graft and that none of the surrounding loose connective tissue is left on it

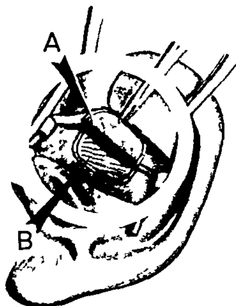


FIG 5
Illustration of operation method Preparation of fascial graft
Principle sketch of the fascial grafting in magnification
A — fascial flap
B — m temporalis.

Grafting technique

A thin, firm, disc-like, nacreous tissue of about the thickness of the drum is obtained This can easily be placed on the pre formed vascular bed (Fig 6) The graft is then covered with a protective cover made of gauze and is then fixed in an exact position by sea sponge packing soaked in antibiotics and cortison (Terracortril ® Pfizer) (Fig 7) The sea sponge is put into place with a firm but not hard pressure The incision is thereafter sutured

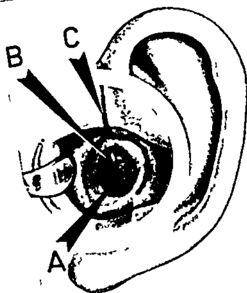


FIG 6
Illustration of operation method Transplantation moment
Principle sketch of A — fascial graft just placed on the transplantation bed covering the perforation,
B — drum
C — incision
in magnification

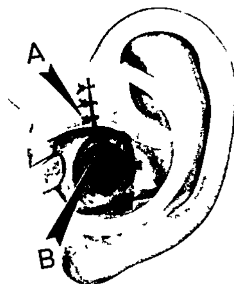


FIG 7
Illustration of operation method Suture and sponge packing
Principle sketch of
A — the sutures done and
B — na[illegible] sponge soaked in cortison — antibiotics, in magnification

Packing technique

The technique in packing the ear canal is a very particular one and needs a comment It is known that sea sponge directly applied on subcutaneous soft parts is able to build up fibroblasts and granulation tissue This ability is so pronounced that the method is used for quick generation of fibroblasts for experimental purposes The protective gauze cover is used to avoid direct contact between the sea sponge and the graft and bed The use of sea sponge has many advantages which make up for the drawbacks mentioned above

1) Thus the use of sea sponge admits of a weak, evenly distributed pressure all over the graft This prevents the pressure in any part from being so high as to inhibit the extravascular circulation of the graft, in which case necrosis immediately occurs This complication is very easily caused by the use of textile packing

2) The sea sponge can also keep moist for a long time, thereby preventing the graft from drying up, which again causes necrosis

3) The sea sponge is loose and allows a certain amount of ventilation In this way anaerobic infections can be avoided, which are not uncommon when textile packing is used Infections of this kind immediately lead to total sloughing of the graft

4) Finally, sea sponge has the advantage over some artificial sponge materials that it is indifferent and not absorbable It thus keeps its original volume and [illegible]

du

Post operative care

The patient is hospitalized for 24 hours post operatively and is thereafter treated as an out patient and not allowed to work The packing of the ear is changed under sterile conditions every 8 day Packing and antibiotics are changed three times in this way After these 3 weeks the patient returns to work In cases where the graft has "taken" but where an air conduction loss remains, politzeration is performed If there is still an air-conduction loss 4 weeks later, puncture of the drum is carried out with a thin cannula and ventilation is performed by inflation with a syringe

The patient is re examined 6, 12, and 24 months post operatively

Results

The results of the present investigation are given in Figs 8 and 9 as pre operative individual case reports Both bone conduction as well as pre and post operative air conduction and healing results are given Every failure is marked

The anamnestic length of the pre operative disorder is given in each case

Fig 8 shows myringoplasties performed with fascia, and Fig 9 a control series of skin grafted cases Fig 8 covers 87 and Fig 9 20 cases For the purpose

of a better surveyability the results have been counted in percentage and are presented in histograms The hearing situation is given both pre- and post-operatively as bone air gap, i e as the difference between the mean figures of the hearing threshold for bone conduction and air conduction in speech frequencies containing 500, 1000 and 2000

Patient		Pre-op data		Post op results					
		Time of disorder years	Hearing	6 months		12 months		24 months	
				Take	Hearing	Take	Hearing	Take	Hearing
I A	350413	19	10/45	+	10/15	+	10/15	+	10/15
R B	510312	4	10/18	+	10/13	+	10/13	+	10/13
SA N	390831	13	10/16	+	10/13	+	10/10	+	10/10
L O	980308	1	13/50	+	11/25	+	13/21	+	13/21
I W	240504	7	11/38	+	11/25	+	11/25	+	11/21
R W	390329	13	10/30		0		0	+	10/10
K S	500704	6	25/56	+	25/30	+	25/35	+	25/35
A S	120401	40	26/63	+	26/53	+	26/48	+	26/53
A S	120401	40	18/60	+	18/35	+	18/35	+	20/30
J S	430204	10	10/18	+	10/10	+	10/10	+	10/10
M S	170619	40	18/60	+	18/20	+	18/30	+	18/28
P S	281012	2	21/36	+	21/36	+	21/36	+	21/36
R S	460429	1	10/11	+	10/11	+	10/16	+	10/11
A. S	420803	1	16/38	+	16/21		0	+	16/22
E S	240910	27	28/46	+	28/31	+	28/31	+	28/33
M P	340916	25	10/25	+	10/11	+	10/11	+	10/11
L P	250206	1	11/15	+	10/10	+	11/10	+	11/10
E P	191215	35	13/36	+	13/30	+	13/30	+	11/36
A P	110930	1	15/28	+	15/17	+	15/17	+	15/17
AK P	531129	8	11/16	+	10/10	+	10/10	+	10/35
S P	081119	40	13/30	+	13/20	+	13/18	+	13/18
S O	930413	1	26/58	+	26/48	+	41/63	+	41/63
KÅ O	420410	10	20/53	+	20/25	+	20/38	+	20/38
K O	950619	45	18/38	+	18/23		0	+	18/16
H O	270721	25	16/41	+	16/28	+	16/36	+	16/31
G A	200815	2	35/65	+	35/85		0	+	35/85
B A	051112	20	25/46	+	25/35		0	+	25/26
A H	190417	20	43/65	+	43/65	+	43/51	+	45/55
B A	440523	10	11/26	+	10/10	+	10/10	+	10/11
V P	391116	10	15/28	+	15/20		0	+	15/23
KA A	450607	12	10/43	+	10/13	+	10/11	+	10/13
S A	390701	1	10/30		0	+	10/15	+	10/10
S J	061112	1	10/15	+	10/10	+	10/15	+	10/15
B J	030430	1	28/50	+	28/30	+	28/35	+	20/21
B J	030430	2	21/45	+	21/35		0	+	21/31
I J	290101	1	11/41	+	11/41	+	11/46	+	11/50
I J	460720	10	10/31	+	10/16	+	10/15	+	10/16
I J	460720	10	10/40	+	10/20	+	10/20	+	10/20
A H	131130	10	10/16	+	10/16	+	10/16	+	10/16
I H	440626	1	10/20	+	10/10	+	10/10	+	10/10
B H	390204	2	10/20	+	10/16		0	+	10/16
A H	280130	3	10/31	+	10/21	+	10/16	+	10/20
M G	370510	15	10/10	+	10/10	+	10/10	+	10/10
MB F	230809	19	15/36		0		0	+	15/15
O E	180528	35	13/28	+	13/16	+	13/16	+	13/20
T D	460905	15	100/100	+	0	+	0	+	0
I D	890528	50	50/60	+	50/55		0	+	50/60
P B	0 0704	40	41/80	+	41/75	+	41/75	+	41/75
F B	16041	5	16/63	+	16/53	+	16/53	+	16/53
S B	2004	0	10/21	+	10/16	+	10/16	+	10/16
S A	905	28	15/30	+	15/17	+	15/20	+	15/17
R A	4 0	4	10/18	—	10/13	+	10/11	+	10/10

Patient	Pre-op data		Post-op results					
	Time of disorder years	Hearing	6 months		12 months		24 months	
			Take	Hearing	Take	Hearing	Take	Hearing
M A 280511	20	10/33	+	10/10		0	+	10/15
H N 020602	1	13/35		0	+	13/23	+	15/23
U N 210906	39	10/21	+	10/11	+	10/11	+	10/11
SÅ N 401021	18	10/25	+	10/13	+	10/13	+	10/11
K N 400524	1	10/25	+	10/11	+	10/11	+	10/11
K N 440131	12	10/46	+	10/35	+	10/31	+	10/35
E N 100128	45	10/35	+	10/20	+	10/26	+	10/21
A.N 070913	15	18/36	+	18/33	+	20/36	+	18/36
A N 480504	4	10/43	+	10/23	+	10/20	+	15/25
N M 240226	1	15/35	+	15/35		0	+	15/20
N M 411113	5	10/15	+	10/11	+	10/11	+	10/11
O L 180615	35	21/61	+	21/36	+	21/36	+	21/50
N L 091007	30	15/36	+	15/23	+	15/23	+	16/23
M L 971125	7	10/30	+	10/30	+	10/30	+	10/30
A.L 190616	33	25/43	+	16/25	+	16/25	+	16/25
B L 440127	14	10/25	+	10/10	+	10/15	+	10/10
A L 981130	4	10/43	+	10/40	+	10/23	+	10/40
A.L 981130	5	10/26	+	11/33	+	10/21	+	10/16
N L 350505	20	10/23	+	10/21	+	10/15	+	10/15
E.L 410926	19	10/30	+	10/25	+	10/30	+	10/13
H F 320227	4	10/21	+	10/10		0	+	10/10
E N 081003	1	23/61	+	23/60	—	23/60		0
S N 010919	40	35/63	—	35/63		0		0
A.H 200907	1	10/16	—	10/16		0		0
A J 090428	15	10/21	—	10/21		0		0
L.O 980308	1	16/50	—	16/50		0		0
G S 110315	40	28/56	—	30/56		0		0
R B 510312	1	10/15	+	10/15	—	0		0
E N 081003	1	20/38	+	20/35	+	20/48	—	20/38
A H 200907	1	10/16		0		0	—	10/16
L.O 980308	1	16/51	+	16/50	—	16/50		0
I J 110822	25	33/65	—	33/47		0		0
O P 420117	5	20/35	—	0		0		0
L.O 980308	1	16/71	+	16/71	—	0		0
O P 420117	8	20/40	+	15/16	—	20/35		0

FIG 8

*Pre post operative hearing table Individual *case report Fascial transplantations
87 cases Takes are given as + failures as — When re examination is not performed on time it is given as 0
Hearing results are given as bone conduction air conduction

Patient		Pre-op data		Post op results					
		Time of disorder years	Hearing	6 months		12 months		24 months	
				Take	Hearing	Take	Hearing	Take	Hearing
G J	080912	1	10/28	+	10/26	+	10/26	+	10/23
I A	281108	13	18/35	+	18/25	+	18/30	+	10/10
K M	420727	1	10/18	+	10/10	+	10/13	+	10/13
G J	450316	11	10/53	+	10/43		0		
A M	131122	6	10/38		0		0		
H B	990627	40	20/35	+	20/35	—	0		0
S J	061112	3	10/28	+	10/13	—	0		0
L I	250206	1	10/35	+	10/16	—	0		0
S B	300624	2	10/48	+	10/18	—	0		0
K M	240226	1	28/40	—	28/35		0		0
H F	040522	2	10/31	—	0		0		0
L L	020306	3	40/93	—	0		0		0
O L	170830	20	20/65	—	0		0		0
A L	981130	2	11/21	—	0		0		0
I J	290101	18	10/30	—	0		0		0
A L	981130	4	10/21	—	0		0		
E C	240910	25	28/46	—	0		0		0
J M	031202	40	16/48		†				
H F	040522	3	20/31	—	0		0		0
I J	110822	30	33/48	—	0		0		0

FIG 9

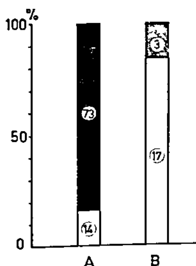
"Pre post-operative hearing table Individual "case report Skin transplantations 20 cases Takes are given as +, failures as — When re examination is not performed on time it is given as 0

Hearing results are given as bone conduction/air conduction

Healing results

In Fig 10 the post operative 24 month healing results are demonstrated in fascia and skin grafting In the whole series, irrespectively of graded tubal function, takes in the fascial graft material constitute 84 % while skin grafts only give 15 % takes

FIG 10

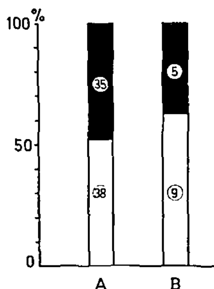


Healing results 24 months post-operatively Per cent histogram
Column A — fascia grafted series (87 cases)
„ B — skin grafted series (20 cases)
Ⓧ — number of cases in the column
■ takes
□ failures

Mastoid cellularity — healing

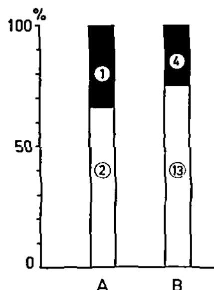
Fig 11 illustrates the relation between cellularity and healing of fascial grafts Out of 73 healed cases 52 % had a small air cell system while the same figure in 14 cases of failure was 63 % It appears from Fig 12 that the corresponding figures in skin grafted cases are 65 % resp 75 %

FIG 11.



Healing — cellularity in fascia grafted series 24 months post-operatively.
Column A — takes (73 cases)
„ B — failures (14 cases)
⊗ — number of cases in the column
Cellularity
■ normal
□ small

FIG 12.

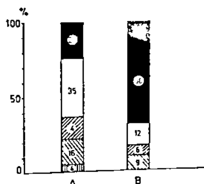


Healing — cellularity in skin grafted series 24 months post operatively
Column A — takes (3 cases)
„ B — failures (17 cases)
⊗ — number of cases in the column
Cellularity
■ normal
□ small

Hearing results

Hearing results are given in Figs 13 and 14 Pre perative hearing as bone-air gap is related to the post-operative 24 month re ults It appears that of fascia grafted cases 69 % show a post operative bone air gap not exceeding 10 dB and 87 % < 30 dB, while the same figures for skin grafting are only 25 % and 80 %.

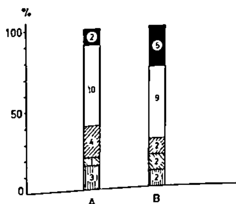
FIG 13



Hearing results 24 months post operatively at fascial grafting bone air gap Histogram 87 cases
Column A — bone air gap pre-operatively
" B — bone air gap post operatively
⊗ — number of cases in the column

0—10 dB ■
11—20 dB □
21—30 dB ////
31—40 dB \\\\
> 41 dB | | |

FIG 14



Hearing results 24 months post operatively in skin grafting bone air gap Histogram 20 cases.
Column A — bone air gap pre-operatively
" B — bone air gap post-operatively
⊗ — number of cases in the column

0—10 dB ■
11—20 dB □
21—30 dB ////
31—40 dB \\\\
> 41 dB | |

Age — hearing — healing

It is clear from Fig 15 that there is a limit at 40 years, beyond which hearing results are markedly worse than in younger cases In the different groups below 40 years the results are obviously very much alike In the case of pre-operative hearing, the situation is similar in all groups except < 10 years Fig 16 shows the relatively good correlation between 6, 12 and 24-month re examinations as far as hearing is concerned By far the greatest majority of per forations in both fascia and skin grafts occur before the 6-month re examination A comparison between healing (Fig 17) and hearing results (Fig 15) shows a good correspondence between bone air gap < 10 dB and takes in the groups < 40 years, but in the group > 41 years the bone-air gap < 10 dB only amounts to 37 % and the corresponding figure for takes is 73 %

In the last group there are 14 cases from 41 to 50 years and among these 7 have a 10 dB bone air gap, while 8 out of 13 in the 51—60 year group and 8 out of 10 in the 61—70 year group do not reach the 10 dB bone air gap Failures are evenly distributed, with 3 in each group

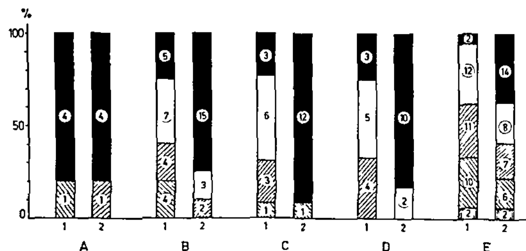


FIG 15

Age hearing histogram fascia transplantation 24 month observation period

Column A — 0—10 years (5 cases) 0—10 dB ■
B — 11—20 (20 „) 11—20 dB □
C — 21—30 „ (13 ,) 21—30 dB ////
„ D — 31—40 (12 „) 31—40 dB \\\\
E — > 41 „ (37 ,) > 41 dB ||||
1 — bone air gap pre-operatively
2 — bone air gap post operatively
Ⓧ — number of cases in the column

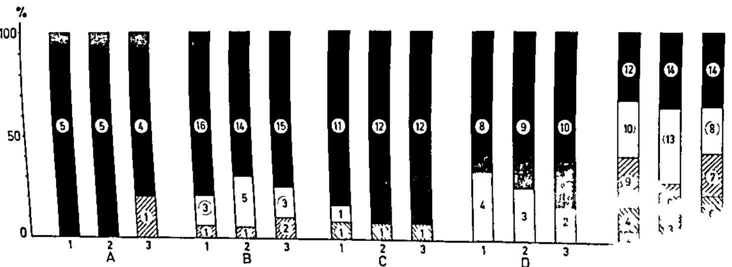


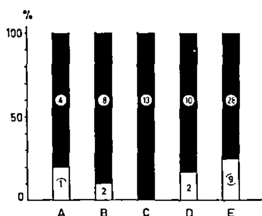
FIG 16

Age hearing histogram, fascia transplantation, 6, 12, 24 month observation period

Column A — 0—10 years
" B — 11—20 "
" C — 21—30 "
" D — 31—40 "
" F — > 41 "
⊗ — number of cases in the column
" 1 — bone air gap 6 months post operatively
" 2 — bone air gap 12 months post operatively
" 3 — bone air gap 24 months post operatively

0—10 dB ■
11—20 dB □
21—30 dB ////
31—40 dB \\\\
> 41 dB ||||

FIG 17



Age healing histogram, fascia grafting, 24 month observation period
Column A — 0—10 years
„ B — 11—20 „
„ C — 21—30 „
„ D — 31—40 „
„ E — > 41 „
Ⓧ — number of cases in the column
■ takes
□ failures

Tubal function — hearing — healing

Out of eleven cases tested for tubal function according to Ingelstedt and Ortegren (1963) during 1961, 9 cases had a tubal resistance of < 10 mm Hg while 1 case had 10—20 mm Hg and 1 case 25 mm Hg tubal resistance One of the cases had a patulous tube and 2 years after operation showed a 12 dB bone-air gap, while the others of this group had a < 10 dB bone-air gap The case with 10—20 mm Hg tubal resistance also had a < 10 dB bone-air gap but in the 25 dB case, the bone air gap is caused by a tubal resistance of 25 mm Hg In these 11 cases there was no failure

General discussion

Myringoplasty has so far mainly been performed with different forms of skin grafts In some places the results obtained were not encouraging enough, so new grafts with better possibilities for healing have been searched for during the last 5 years Thus in 1957 the author began to use fascia grafts, which in plastic surgical literature are said to have certain advantages

Healing results

Comparison of results to those of previous authors is very difficult since no uniform standards have been published and the time of observation, if given at all, varies widely. In most cases, furthermore, the entire series are not re-examined. The present author is of the opinion that both healing and hearing results must be published as long term results with an observation period of at least 24 months. Up to 1959 the results are mainly, for natural reasons, given as immediate post-operative results. If Zollner's (1957) post-operative 9 failures out of 52 cases are compared to the present author's 100 % takes 1 month after operation, the inadequacy of this way of providing results is clearly apparent: in the author's series the 100 % takes in the 1-month results turn out to change to 84 % takes 24 months post-operatively. Wright (1956) reports 40 takes out of 56 cases re-examined 3—36 months post-operatively. The observation period of the failures is not mentioned.

Bandtlow (1960) re-examined 80 out of 322 operation cases for hearing 36 months after operation. In Agazzi's material (1960) there were 18 % failures 12 months after operation, but in his series there were another 15 % with a moist ear. The origin of this complication is not given.

It is much easier to make a comparison with the results given in an exemplary way by Livingstone *et al.* (1961). All cases including 70 % takes have been re-examined 6 months after operation. Vein grafts were used. For a re-examination period of 18 months Heermann (1962), using fascia grafts, gives 50 takes out of a material of 55 cases. These figures are similar to those of the present author.

Zollner seems to provide a support for the present author's method when stating that two years ago he substituted fascia grafts for skin grafts because of too frequent complications with "Lappencholesteatom" and inexplicable perforations. Wullstein, too, has reported that some years ago he changed his technique and now uses a combination of fascia and skin.

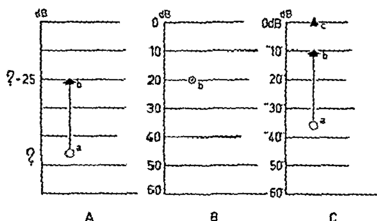
Hearing results

The difficulties of mutually comparing operation results published as dB hearing gain, post-operatively remaining hearing loss or dB bone air gap, are obvious.

If only post-operative hearing improvement is given, the reader has no possibility of evaluating the results unless pre-operative hearing loss and bone conduction are also given. Mere hearing loss is also very hard to read, if the above mentioned pre-operative factors are not published simultaneously. It is certainly possible to find out if the patient attains social hearing or not, but it is impossible to tell whether this is satisfactory or not from the point of view of operation.

In Fig 18 it is seen from part A how improvement is marked as a—b From this account it cannot be read where in the audiogram this hearing improvement is located, nor if there is any possibility for further improvement, since neither pre-operative hearing, a, nor bone conduction has been published

FIG 18



Principle sketch of different ways of giving hearing results
A — hearing improvement method
B — remaining hearing loss method
C — pre and post operative bone air gap method
a — pre-operative air conduction
b — post operative air conduction
c — bone conduction

In part B, an account of remaining hearing loss is exemplified Results are often given as e g "reached the 30 dB line" or "attained social hearing". This way of giving results is justified if a certain operation series is regarded from a social point of view, but provided no information on the value of the operation method for restoring the sound transmission of the middle ear in a normal condition

In part C an account of pre and post-operative bone air gap is exemplified A study of the change of a—c pre-operatively into b—c post-operatively explains how operative treatment has managed to restore sound transmission ear canal — cochlea The position of c is not determined but is here given as "0 dB" If the real figure of the bone conduction is added, the reader has access to all information he may need for evaluating the prognosis of a certain case

According to the author, measurement of the bone-air gap provides the best information on the results of tympanoplasty This is the only way of recording the effect of the surgical treatment directly from the middle ear function without interference of the cochlear component

At myringoplasty with an intact ossicle chain the bone-air gap should theoretically be 0 dB For this reason the author has called all cases with a bone-

air gap of less than 10 dB "good results" What is said about a 24 month follow up in healing results is also true of hearing results The author's 69 % 10 dB bone air gap can quite well be compared to Bandtlow's 66 % 15 dB These are long term results

Causes of failures

The rôle of tubal function

It seems likely that the results given by the author would have been essentially better if a more thorough selection of operation cases had been made, ruling out all cases except those with good tubal function Exact, objective methods for measuring tubal function have been worked out by the author *et al* They have not been used practically until long after this investigation began, so only 11 cases have been examined for tubal function by this method This is why it has not yet been possible to draw any conclusions, but all cases intended for operation are now being examined in this way

The role of infection

It is quite natural that a dry ear, i e an uninfected one, should be of great importance since post operative infection increases the risk of failure Ye (1957) has studied the effect of infection upon split skin grafts used for covering skin defects He makes it clear that the number of takes is a function of pH in the vascular bed, pH 7,6 giving 100 % takes, while the percentage sinks continuously with a decreasing pH down to 7,0, where the takes is 0 % He also shows that the pH is a function of the infection of the surface of the vascular bed, sterile surface giving pH 7,6, while an increase of bacterial concentration causes a pH decreasing towards and even below 7,0 He does not demonstrate any difference between different infections or different degrees of virulence A thorough pre operative treatment of the ear and infection prophylaxis are therefore very valuable

It is well known that almost all skin is contaminated and that sterilization of skin is extremely difficult This fact would seem to be one of the reasons for the high percentage of failures in skin transplantation From this point of view the sterile fascia is preferable Basing his opinions on Billingham's investigations, Link (1960) pointed out the risk of auto immunization by using grafts containing epithelium This fact may explain Heermann s (1962) observation of allergic running ears as a result of skin transplantation The risk seems not to be present when connective tissue grafts are used, which is one more reason why fascia should be preferred

Mechanical causes

Skin contains elastic fibres This is a mecha al drawback since skin curls and rolls and is difficult to adapt to the vascu bed diminishing the contact of the surface with nourishing tissue and increa ng the risk of bleeding and

consequently, of failure A too hard and inadequately applied packing of the ear canal for fixing the graft to the vascular bed is also risky, because it inhibits the capillary circulation of the vascular bed and the extra-vasal circulation in the graft It seems reasonable that the pressure of the packing in the ear must fall far below the pressure difference of arterial and venous capillary blood pressure, so that circulation and nutrition are not interfered with The use of sea sponge gives the advantage of a continuous, loose and evenly distributed pressure applied throughout the time of treatment It does not change its volume by absorption, permits ventilation, and thus precludes anaerobic infection In the present series no infection was observed during the post-operative care

Actual fascia grafted series

It seems likely that a long anamnesis of chronic otitis pre operatively can cause damage to the Eustachian tube resulting in hearing disorders In the actual fascia grafted series 19 out of 27 cases not gaining a post-operative bone air gap < 10 dB had anamnestically suffered from chronic otitis for > 5 years It may be that the previously observed high percentage of failures in cases of myringoplasty aged above 40 is simply due to a possibly longer anamnesis of chronic otitis In the present investigation this is valid fo rhearing results but not for healing

Among the 14 re perforations in fascia grafts there are only 2 caused by infection, acute otitis 6 respectively 12 months post operatively Since there were no failures 1 month after operation, mechanical causes in connection with the treatment need not be discussed Nine of the remaining cases were > 40 years old There is reason to believe that these old patients have a long anamnesis of their disorders, but 5 out of 9 had an anamnesis of only 1 year In 1 case hearing loss occurred during swimming and some days later a perforation, possibly of traumatic origin, was found In the 2 remaining failures no cause could be discovered

Conclusions

In the present paper the following views are stated

1) that connective tissue grafts, i e fascia, seem to be superior to skin grafts in myringoplasty,
2) that results of myringoplasty performed on 40-year old patients are not so good as those below this limit and that this is most obvious in the case of hearing results,
3) that re perforations mostly occur before the 6-month re examination and that hearing results do not change much after this examination,
4) that a graded, objective method for measuring tubal resistance is required for judging the prognosis of myringoplasty,
5) that the role of the mastoid cellularity in myringoplasties is not clear and that direct, volumetric methods for volume determinations of the functioning air cell system must be used

SUMMARY

The present study describes a method for myringoplasty with fascia from m temporalis as graft (preliminary report 1959) The material consisted of 87 ears treated with myringoplasty Fascia was used as graft and was followed up for 24 months post operatively both as regards healing and hearing results
Pre- and post operative measures are described, above all where infection prophylaxis has been performed The patients have only been examined for tubal passage, or not pre operatively, and attempts to grade the function of the Eustachian tube have only been made in 11 cases during 1961 The operation technique is described and the necessity for a traumatic grafting is emphasized, as is also the importance of a properly made packing of the ear canal for fixing the graft The results are described as "takes" in 84 % without grading of the tubal function, and as post-operative "bone air gap" of < 10 dB in 69 %, also without grading of the tubal function. The relation between healing and cellularity is described and discussed, so is the effect of age on post operative hearing and healing results The importance of post operative infection is discussed and also the causes of "failures" The importance of tubal function, cellularity, and the value of exact and objective method for determining these factors are similarly discussed

Zusammenfassung

Eine Methode der Myringoplastik mit Verwendung der Fascia m temporalis wird beschrieben Die Arbeit umfasst 87 Falle, bei denen Fascia als Material zur Myringoplastik verwendet wurde 24 Monate nach der Operation wurden Einheilung und Horfunktion bei den oben genannten Fallen nachuntersucht

Die pra- und postoperativen Massnahmen werden unter besonderer Betonung der Infektionsprophylaxe beschrieben Das Patientenmaterial wurde praoperativ darauf untersucht, ob eine Tubarpassage vorlag oder nicht Der Versuch einer graduierten Beurteilung der Funktion der Tuba Eustachii wurde nur in 11 Fallen im Jahre 1961 gemacht Die Operationsmethode wird beschrieben, und man hebt die Bedeutung des atraumatischen "grafting" hervor ebenso wie die Wichtigkeit einer einwandfrei ausgefuhrten Tamponade des Gehorgangs fur die Fixierung des Transplantates Die Resultate werden teils als "takes" in 84 % ohne Graduierung der Tubarfunktion beschrieben, teils als postoperatives "bone air gap" mit $<$ 10 dB in 69 % Fallen, auch hier ohne Einteilung der Tubarfunktion Das Verhaltnis Heilung — "Cellularity" wird diskutiert und der Einfluss des Alters auf die postoperativen Gehors- und Heilungsergebnisse Die Bedeutung der postoperativen Infektionen wird hervorgehoben, ebenso die Ursachen von "Versagern" ("failures"). Schliesslich werden die Tubarfunktion und das lufthaltige Zellsystem in ihrer Bedeutung besprochen und der Wert von exakten und objektiven Methoden zur Bestimmung dieser Grossen hervorgehoben

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From the Anatomical Institute University of Oslo (Head Professor Jan Jansen M.D.)
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PREFACE

This investigation has been carried out in the Anatomical Institute, University of Oslo, under the guidance of the head of the Institute, Professor Jan Jansen, M D It is a great pleasure to acknowledge my profound indebtedness to Professor Jansen for the opportunity to work in the Institute, for his inspiring interest, critical advice and generous aid

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INTRODUCTION

It is a well known fact that neonatal asphyxia is responsible for a variety of neurological disorders appearing in later life (Little 1862, Clifford 1941, Darke 1944, Nielsen and Courville 1951, Corner and Anderson 1958, MacKinney 1958, Windle 1961, 1963 a, b) but only a few controlled human studies (e g Schreiber 1938, Dublin and Brown 1942, Courville and Marsh 1944, Christensen 1956, Cammermeyer 1958, Malamud 1963) and not many animal experiments (e g Ford 1928, Gildea and Cobb 1930, Thorner and Lewy 1940, Weinberger *et al* 1940, Windle *et al* 1944, Windle 1963 a, b) have been carried out to assess the extent of damage in the central nervous system of the new-born None of these authors have paid special attention to the auditory pathways in asphyxia Clinical observations indicate a selective vulnerability of the auditory pathways, since a common, perhaps the most common, sequela in children surviving a condition of neonatal asphyxia is a hearing loss This is always of the same type audiometrically, the bilateral, high frequency, sensorineural type (Fisch and Osborn 1954, Fisch 1955, 1956, Flottorp *et al* 1957, Barr and Klockhoff 1959, Aurup 1959, Zaner and Miller 1959) This typical pattern of the audiograms and the neonatal asphyxia common to all these cases give us reason to suspect a damage inflicted upon the sensory cells of the cochlea or the nerve cells of the auditory pathways

The object of the present investigation is to produce data that will throw light upon the pathogenesis of these clinical findings It is an attempt to demonstrate where the damage is inflicted, and to what extent degenerations of the auditory pathways are demonstrable in cases of asphyxia neonatorum

It may be objected that 'asphyxia' is an incorrect term, as the word etymologically means a state of pulselessness (Schwartz 1961) Anoxia or hypoxia would be more correct, however, asphyxia and asphyxiation are used here on account of the extensive use of these terms both clinically and in the literature Asphyxia denotes a disturbance of the oxygen supply Clinically asphyxia or asphyxiation is characterized by an interruption in breathing sometimes culminating in suffocation

MATERIAL AND METHODS

The human material

The human material consists of 60 brains and 94 temporal bones from the same individuals, 45 pairs and 4 single

In 11 cases the temporal bones were not available

Nine of the 60 brains serve as controls These brains are derived from cases in which the central nervous system presumably was normal

Of the remaining 51, five are excluded from the material because of accidents during the preparation of the cochlear nuclei, in four a part of these nuclei was cut off during preparation, and in one case the brain stem was by accident cut in sagittal sections which proved inadequate for comparison

One brain was accidentally destroyed

In six other instances a cell count has been performed, but two of these were considered too old to represent control cases (31 and 34 years) and four presented additional factors besides asphyxia which could have produced nerve cell destruction commotiones cerebri, acute nephritis, intoxication during pregnancy, and excessive saline injections

This leaves 39 brains from children fatally asphyxiated, and 9 in which the anoxic period was negligible as a cause of a nerve cell loss

Ninety four temporal bones were obtained From the 39 asphyxiated children both temporal bones were obtained in 35, one in two, and none in two cases Both temporal bones were obtained in five of the controls This makes a total of 82 temporal bones

The remaining 12 temporal bones belong to cases discarded from the material, 8 because of accidents in the preparation of the cochlear nuclei, which are of vital importance for the comparison, and 4 belonged to the cases presenting additional factors besides asphyxia

The gestational age of the asphyxiated babies at birth is evident from Table 1

TABLE 1

Full term or overdue	0–1 month premature	1 2 months premature	2 3 months premature	> 3 months premature
6	6	10	11	6

The survival time ranges from 4 hours and 18 minutes, up to 22 days. During this time the babies were all asphyxiated to various extents, and treated in an incubator where the supply of oxygen could be controlled. As usual in such cases, the attacks of asphyxia occurred periodically, so that additional treatment, such as artificial respiration, had to be given. In many instances a gastric tube was inserted, supplying oxygen. More specific data concerning these babies are reported in the case histories.

Collection and preparation of the human material

The doctor or nurse on duty in the respective hospital departments called the author immediately after death had occurred, in order that fixation by perfusion could be performed as soon as possible.

In a study like the present one, it is of the utmost importance that post mortem artifacts are excluded. This especially concerns the fragile cells of the organ of Corti. By special permission, 45 brains could be intra arterially injected, 25 of these were injected less than 2 hours post mortem, 14 between 2–4 hours, 5 between 4–6 hours and the remaining 10 hours post mortem.

For various reasons, 4 of the asphyxiated babies and 8 of the controls could not be fixed by perfusion. The bodies, however, were stored in refrigerators until the brains were removed, which was always in the morning following death.

Method of perfusion

After transection of the costal cartilages the sternum was elevated, the pericardium opened, and the ascending aorta dissected free. The aorta was ligated between the left subclavian artery and the Botallian duct, and the two internal mammary arteries were clamped. Through a little slit in the ascending aorta a tulip needle was inserted, and the artery ligated around its shaft. The needle could then be easily pushed up on either side, to perfuse the left subclavian artery, the left common carotid, and the innominate artery. To allow unobstructed flow, a cut was made in the superior vena cava or sometimes in the right atrium.

The blood left in the brain was first rinsed out by infusion of some 300–400 cc of isotonic saline. Following the saline perfusion the fixing fluid was injected. Both the saline and the fixing fluid were kept in a glass container with a rubber tubing attached to it, placed at a height above the operating table equalling a pressure of 90 cm water and the temperature of the solutions was 37° Celsius.

In the first 24 cases, 10% formaline was used for fixation, but, as formaline proved to give very poor fixation of the inner ear, the Heidenhain Susa fixation was used later on. This solution consists of

Sublimate	45 g
NaCl	5 "
H_2O	800 cc

Trichloracetic acid	20	cc
Formaline 10 %	200	»
Glacial acetic acid	40	»

During the post-mortem examination, the brain was carefully removed, the brain stem being severed as far caudally as possible, and the VIIIth nerve at its entrance into the internal acoustic porus

The time between arterial perfusion and removal of the brain varied between 6 and 12 hours

After about a week blocks of tissue were removed from the following subdivisions of the brain Medulla oblongata with the cochlear nuclei, the inferior colliculi, the medial geniculate bodies and the acoustic cortical areas in the anterior transverse temporal gyri

After 14 days in 96 % alcohol the blocks were dehydrated, embedded in paraffin and cut in transversal sections at 15 microns Every 10th section was mounted and stained with thionine

Preparation of the cochlea

The part of the temporal bone containing the labyrinth was removed using a high speed circular bone saw, which cuts through the bone nearly without any pressure being applied

After removal of the block, a paracentesis was performed and a circular saw attached to a dentist s burr was used to open the vertical arch of the bony labyrinth These operations were performed in order to allow the fixation fluid an easier access to the inner ear, whereupon the block was again placed in the fixation bath for at least a week Perfusion with formaline did not give satisfactory results Among the 22 cases prepared in this way, only 8 proved suitable for histological evaluation In all cases, however, where the Heidenhain-Susa solution was used as fixative the preservation of the organ of Corti varied from fairly good to excellent

After completed fixation the following procedure was employed

1 Decalcination, trichloracetic acid 5 % changed every other day for four weeks		
2 Running tap water	24 hrs	
3 5 % neutralized Sodium sulfate	» »	
4 Washing in gas free distilled water	» »	
5 35 % alcohol gas free	» »	
6 50 % » »	» »	
7 60 % » »	» »	
8 70 » »	» »	
9 96 » not gas free	48 »	changed twice
10 100 » for three days, changed three times		
11 Ether Alcohol 100 % for two days, changed twice		
12 Thin Celloidin	14 days	
13 Thick »	» »	

14 Chloroform/Alcohol 100 % till the block sinks, approximately 2 hrs
15 Chloroform 24 hrs, changed once
16 Paraffin 3 days, changed every day, temp 54–56° C

Computation of the number of cells in the cochlear nuclei

The procedure involves two different steps
a) Counting of the number of cells in a measured volume, a 'unit' of the nuclei, and
b) calculating the total volume of the nuclei

a) The measured unit consisted of a square photographed onto a translucent film This was placed in the ocular piece of the microscope The square was photographed from a Zeiss Ocular netzmicrometer, and enlarged, so that at × 320 magnification one square occupied practically the entire optic field

Calibrating this square with a Zeiss 5 + 100/100 object micrometer, the sides measured 0 22 mm, and the square area then measured 0 0484 mm²

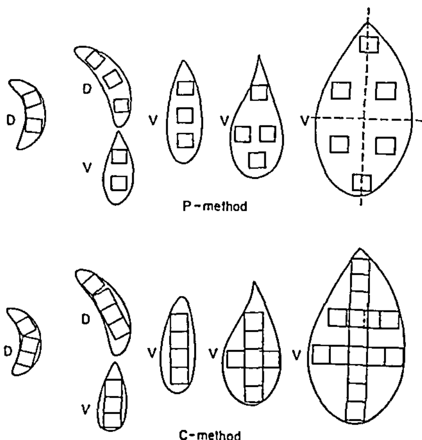


Fig 1 The two methods applied for placing the units D — dorsal nucleus V — ventral nucleus

of the liver, kidneys, spleen and diaphragm Haematothorax and haematoperitoneum Brain W 1570 g Haemorrhagia subarachnoidalis, otherwise the brain was intact, no pathological findings in the medulla oblongata macroscopically

34) Male, 5 months, twin Normal, but somewhat premature delivery Normal development, no earlier diseases Suffocated by vomiting while mother was busy feeding the other twin Died immediately Perfusion not performed. Autopsy Small haemorrhages on the surface of the somewhat dilated and congested lungs The thymus enlarged, W 28 g Brain W 700 g Macroscopically no pathological findings

39) Female, 19 months Born at term, normal development 17 months old acute otitis, of short duration Treatment paracentesis and antibiotics Control showed normal conditions of the ear drums Two days before death the child seemed to be ill The ears were again controlled, normal findings The night before death vomiting and symptoms of intoxication At 5 o'clock in the morning she was gabbling, and when the father went to work she slept, the father heard the somewhat irregular respiration. At 9 o clock she was admitted to hospital but was dead on arrival Perfusion not performed Autopsy Invaginatio ileocoecalis Normal lungs, normal conditions in the middle ear and the mastoidal cells Brain W 1250 g No pathological findings macroscopically

45) Male, 2½ years, normally developed Strangled by the harness used for keeping him in bed Found still warm by the parents Artificial respiration without effect Perfusion not performed, placed in a refrigerated room, and autopsy performed the next morning W 18 kg, L 90 cm Autopsy Lungs pink coloured with numerous subpleural petechial haemorrhages Sanguineous foam in the bronchi and the trachea. Haemorrhages in the pericardium Brain W 1370 g Slightly oedematous No haemorrhage or other pathological signs found

51) Female, fifth child normal pregnancy Birth about 1 month, 9 days premature or less, when labour started Transverse position of the foetus, the child turned and a foot brought down Specifications of narcosis not mentioned The child feeble, no movements, pale, but heart action about 60 min Some gasping movements Oxygen administration, transfusion of 25 ml blood, intubation, all without effect, the child lived for 35 minutes only Perfusion 2 hrs, 45 min post mortem Autopsy The lungs atelectatic Brain W 300 g Subarachnoidal haemorrhage around the fissura parietooccipitalis, blood clots in the posterior part of the fissura longitudinalis, down to the tentorium cerebelli

57) Female 13½ years committed suicide by inhaling gas, after failing to cut the arteries of the left wrist. Intubation, suction, artificial respiration and heart massage in vain Perfusion not performed the body placed in the refrigerator till the next morning Autopsy Petechial haemorrhages in the parenchymatous organs, pink colour of the fluent blood, otherwise normal findings Brain W 1550 g A pink colouring induced by the blood, otherwise normal findings macroscopically An audiogram performed at school some years before showed normal hearing

59) Female 17 years, killed about 7 o'clock in the evening in a traffic accident Brought directly to hospital where death was confirmed Perfusion not permitted, refrigerated, autopsy performed the next morning Autopsy Fracture of the basis cranii and aspiration of blood into the right lung Brain Multiple small haemorrhages and a considerable oedema cerebri Hearing tests performed while at school 8 and 11 years earlier showed normal hearing at that time

60) Male 15 months killed by a car running over his head Brought immediately to hospital, where a puncture was performed and blood mixed with brain tissue was aspirated Numerous fractures of the skull found Artificial respiration performed but the heart action ceased

4 hrs 25 min after the accident The body was placed in the refrigerator and autopsy performed the next morning Brain The right hemisphere partly crushed, extensive haemorrhage in the brain tissue and in the pia The medulla oblongata seemingly intact

Asphyxiated cases

The case numbers correspond to the Table numbers If not especially mentioned, the mothers were medically examined regularly, were Rhesus positive, and had no complications during pregnancy They received no extra medication which could possibly influence the child, and no narcosis was given during delivery

Presentations other than the common cephalic are especially mentioned, also signs of eventual intrauterine asphyxia The asphyctic babies were, as a rule, treated in the following way aspiration, suction through the larynx and oesophagus, oxygen administration *ad modum* Åkerren (1947) and in the incubator, either the American Isolette C-35, or the Dutch Maseynec Injection of K tamin, Nyco, 1 ml i m immediately following delivery

When attacks of asphyxia became more severe, first cutaneous stimulation, then artificial respiration, mostly mouth to mouth respiration and aspiration were repeatedly performed The Moro reflex, the instantaneous flexion of particularly the upper extremities in normal new born, by different stimuli, was positive unless otherwise stated After death, the first brains, including No 24, were perfused with formaline, later the Heidenhain Susa solution was used

2) Female, first born, mother hypercholesterolaemia and angina pectoris Normal progress of the pregnancy during the first 7 months Two months and 10 days before term however eclampsia was threatening and in Curacit ether narcosis a caesarean section was performed The baby cried at once W 1500 g L 40 cm Cyanotic and asphyctic throughout survival 19 hrs and 57 minutes Perfusion 2 hrs post mortem Autopsy Atelectasis of both lungs Brain W 300 g Macroscopically no pathological findings

3) Male second birth first delivered twin Term uncertain probably about 3 months premature W 1450 g L 44 cm Cried immediately but was cyanotic Lived 9¼ hrs asphyxiated all that time Perfusion 4 hrs post mortem Autopsy Total atelectasis of the lungs perforation of the curvatura minor ventriculi (the gastric probe for oxygen administration) Brain W 170 g Moderate subarachnoidal haemorrhage at the base of the cerebellum and the parieto-occipital regions Some blood stained fluid in the ventricular system

4) Male twin brother of No 3, delivered 15 min later W 1290 g L 40 cm Cried immediately but was cyanotic Lived 9 hrs, 5 min, asphyctic all that time Perfusion 3¾ hrs post mortem Autopsy Hyaline membranes and atelectatic lungs Brain W 190 g Macroscopically no pathological findings

5) Female second born mother two previous abortions Small haemorrhage in the second month otherwise a normal pregnancy Delivery 3 months and 6 days premature, delivery lasting 17 hrs Cried at once W 930 g L 35 cm Asphyxiated during life, died at 11 hrs 55 min Placed in a refrigerator 4° Celsius perfusion performed 10 hrs 15 min post mortem Autopsy Atelectasis of the lungs Brain W 200 g Some blood in the lateral ventricles and some minor haemorrhages in the cerebellar substance

7) Male, third born, 3 months, 6 days premature W 1010 g, L 36 cm Asphyctic and cyanotic Ilotycin treatment on account of pustulae colli Weight fell to 710 g on the 5th day of life Lived 5 days and 20 hrs, asphyctic all that time Several grave attacks relieved by mouth to mouth respiration Perfusion 6 hrs, 50 min post mortem after cooling of the body Autopsy Hydronephrosis of the left kidney, otherwise no pathological findings Brain W 110 g The third ventricle, the lateral and the fourth ventricles filled with coagulated blood

10) *Female, first born, breech presentation about two months before term W 1140 g L 37 cm* Lived 1 day, 8 hrs, 5 min, in rather good condition for the first 10 hrs, but thereafter asphyctic *for about 22 hrs* Perfusion 5 ½ hrs post mortem Autopsy No pathological findings Brain Subarachnoidal haemorrhage around the pons, and on the convexity of the right hemisphere (about 1 × 1 cm)

11) Female, second twin mother an abortion one year previously Mother Rhesus negative, father Rhesus positive No antibodies found in maternal blood in the 6th month of pregnancy Spontaneous delivery foot presentation Syntocinon 5 I U, no other medication Prematurity 1 month, 3 weeks, born 7 minutes after the surviving twin, which was a breech presentation W 2020 g, L 43 cm Cyanotic, pressing respiration Lived 1 day, 4 hrs, 48 min, asphyctic all the time Perfusion 5 hrs post mortem Autopsy Lungs appeared somewhat congested, but were floating on water On microscopic examination considerable atelectasis was found, many alveoli were collapsed, many containing hyaline membranes, alternating with areas of emphysema Brain W 270 g No pathological findings macroscopically

12) Male, first-born Born in a private midwife institution Term and Rhesus relations not exactly known Approximate prematurity 2½ months W 1710 g, L 43 cm Cried weakly at first, better after bathing Admitted to hospital the next day on account of asphyxia and cyanosis Lived 1 day, 11 hrs, 14 minutes asphyxiated for about 12–13 hrs Perfusion 3 hrs, 15 min post mortem Autopsy Considerable atelectasis of the lungs, some petechial haemorrhages in the lung parenchyma Brain W 235 g Subarachnoidal haemorrhage on the posterior aspect of the cerebellar hemispheres and around the left vena terminalis

14) Male seventh child, second twin Uncomplicated delivery of 5 hrs duration, 10 days before term Lived 3 days 1 hr 15 min, asphyxiated intermittently during the last 28 hrs Perfusion 2 hrs post mortem Autopsy No definite pathological findings Brain W 300 g Macroscopically no pathological findings

16) Male second child term unknown to mother Birth unexpected during vacation trip in the country A midwife called in time to accept the placenta Child quickly hospitalized due to cyanosis Mongoloid features observed on admittance W 1470 g, L 39 cm The first two days in hospital free respiration when oxygen was administered, later cyanosis and a strained respiration developed Bilirubin (serum) 14 2 mg/100 ml on the 4th day, and blood exchange transfusions were performed Systolic murmur heard over the heart Lived 16 days, asphyxiated intermittently for the last 14 days Perfused 3 hrs post mortem Autopsy Atelectasis of the lungs otherwise no pathological findings Brain W 176 g No haemorrhage, no icteric staining

17) Female second child mother neurosis and pyelitis during pregnancy, antibiotic treatment Small haemorrhage in the 6th month of the pregnancy hospitalized Uncomplicated delivery of 5 hrs duration 2 months and 18 days premature Breech presentation W 1610 g L 40 cm Lived 10 hrs 30 min asphyxiated all the time Perfusion 1 hr 40 min post mortem Autopsy Atelectasis of the lungs which were sinking in water Brain W 170 g Smaller subarachnoidal haemorrhages around the brain stem and over the cerebral hemispheres

18) Male, no information about the family, except the mother being Rh pos Uncomplicated delivery lasting only one hour One month 11 days premature W 1850 g L 42 cm Normal respiration the first day, later respiratory distress with a severe cyanosis, and a slight icteric staining of the skin developed Penicillin Streptomycin administered on account of crepitation heard over the lungs Dosage not mentioned The last day sanguineous froth around the mouth, and some convulsions Lived 2 days, 4 hrs, and 20 min, asphyxiated for approximately 1 day, 6 hrs Perfusion 3 hrs, 10 min post mortem Autopsy Considerable atelectasis of the lungs Brain W 255 g No macroscopically visible pathological changes No icteric staining

19) Male, second child, uncomplicated delivery during transportation to hospital Respiratory distress with cyanosis developed immediately W 1750 g, L 42 cm Breech presentation Lived 13 hrs, asphyxiated all the time During the final hrs haemorrhagic expectoration Perfused 1 hr, 10 min post mortem Autopsy Moderate atelectasis of the lungs, which floated on water Haemorrhage in the suprarenal glands Brain W 250 g A blood clot the size of a pea found in the rostral part of vermis inf, otherwise normal findings macroscopically

20) Female, first born, placental bleeding 2 months before term caesarean section, Pentothal-Curacit narcosis W 1500 g L 40 cm The child cyanotic, cried weakly Asphyxia and cyanosis continuously all of its lifetime, 1 day, 8 hrs, 5 min. Perfusion 2 hrs post mortem. Autopsy No pathological findings Brain A blood clot the size of a pea in the cisterna magna The ventricular system filled with blood Otherwise no pathological findings

21) Male, first born, 2 days overdue, duration of delivery 9 hrs W 2900 g, L 49 cm Normal development until 2 days postnatally, when asphyxia and cyanosis occurred Lived 2 days, 14 hrs, 30 min asphyxiated approximately 11 hrs Perfusion 2 hrs post mortem Autopsy Haemorrhagia pulm Brain W 470 g Macroscopically no pathological findings

22) Female, fourth child, ninth pregnancy No information about conditions during pregnancy, but due to bleeding from a placenta praevia, a caesarean section was performed about 14 days before term Anaesthetic Citopan 0 2 g, Curacit 50 mg W 1530 g, L 42 cm The child cried at once, and had no respiratory trouble before 5 hrs postnatally when attacks of asphyxia started In addition to the standard treatment Cardiazol and Pentazol were administered Lived 12 hrs, 6 min, asphyxiated for the last 7½ hrs Perfusion 1 hr post mortem Autopsy Atelectasis of the lungs Brain W 200 g No abnormalities macroscopically visible

23) Male second child After a fall, labour and haemorrhage started and birth took place 1 month, 28 days before term W 1600 g, L 41 cm Cried immediately but became asphyctic after about an hr Lived 1 day, 14 hrs 4 min, asphyctic for about 1 day, 7–10 hrs Perfusion 2 hrs post mortem Autopsy Numerous small haemorrhages found in the pericardium, the lungs atelectatic sinking in water Brain W 225 g No macroscopically visible abnormalities

24) Male second child mother also one abortion During the pregnancy, small haemorrhage at about mid term, otherwise normal conditions Term not exactly known After 4 hrs of labour, a macerated foetus of 650 g was delivered, and a twin, male W 1000 g, L 35 cm, was [illegible]

Autopsy Low content of air in the lungs, which sank in water Brain W 200 g No macroscopic pathological findings No icteric staining

26) Male second child, delivered 1 month, 11 days prematurely W 2150 g, L 43 5 cm The child cyanotic with feeble cries and a strained respiration Some vomiting Spinal puncture Haemorrhagic spinal fluid Lived 1 day, 8 hrs, asphyctic all the time Perfusion 1 hr, 40 min

7) Male, third born, 3 months, 6 days premature W: 1010 g, L: 36 cm. Asphyctic and cyanotic. Iliotycin treatment on account of pustulae colli Weight fell to 710 g on the 5th day of life. Lived 5 days and 20 hrs, asphyctic all that time Several grave attacks relieved by mouth to mouth respiration Perfusion 6 hrs, 50 min post mortem after cooling of the body Autopsy. Hydronephrosis of the left kidney, otherwise no pathological findings Brain W: 110 g The third ventricle, the lateral and the fourth ventricles filled with coagulated blood.

10) Female, first-born, breech presentation about two months before term. W: 1140 g, L: 37 cm Lived 1 day, 8 hrs, 5 min, in rather good condition for the first 10 hrs, but thereafter asphyctic for about 22 hrs Perfusion 5 ½ hrs post mortem Autopsy. No pathological findings. Brain: Subarachnoidal haemorrhage around the pons, and on the convexity of the right hemisphere (about 1 × 1 cm)

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7) Male, third born, 3 months 6 days premature W 1010 g L 36 cm Asphyctic and cyanotic Hotvein treatment on account of pustulae colli Weight fell to 710 g on the 5th day of life Lived 5 days and 20 hrs, asphyctic all that time Several grave attacks relieved by mouth to mouth respiration Perfusion 6 hrs, 50 min post mortem after cooling of the body Autopsy Hydronephrosis of the left kidney, otherwise no pathological findings Brain W 110 g The third ventricle, the lateral and the fourth ventricles filled with coagulated blood

10) Female, first born, breech presentation about two months before term W 1140 g, L 37 cm Lived 1 day, 8 hrs, 5 min, in rather good condition for the first 10 hrs but thereafter asphyctic for about 22 hrs Perfusion 5 ½ hrs post mortem Autopsy No pathological findings Brain Subarachnoidal haemorrhage around the pons, and on the convexity of the right hemisphere (about 1 × 1 cm)

11) Female, second twin mother an abortion one year previously Mother Rhesus negative, *father Rhesus positive No antibodies found in maternal blood in the 6th month of pregnancy* Spontaneous delivery, foot presentation Syntocinon 5 I U, no other medication Prematurity 1 month, 3 weeks, born 7 minutes after the surviving twin, which was a breech presentation W 2020 g, L 43 cm Cyanotic, pressing respiration Lived 1 day, 4 hrs, 48 min, asphyctic all the time Perfusion 5 hrs post mortem Autopsy Lungs appeared somewhat congested, but were floating on water On microscopic examination considerable atelectasis was found, many alveoli were collapsed many containing hyaline membranes, alternating with areas of emphysema Brain W 270 g No pathological findings macroscopically

12) Male, first born Born in a private midwife institution Term and Rhesus relations not exactly known Approximate prematurity 2½ months W 1710 g, L 43 cm Cried weakly at first, better after bathing Admitted to hospital the next day on account of asphyxia and cyanosis Lived 1 day, 11 hrs, 14 minutes, asphyxiated for about 12–13 hrs Perfusion 3 hrs, 15 min post mortem Autopsy Considerable atelectasis of the lungs, some petechial haemorrhages in the lung parenchyma Brain W 235 g Subarachnoidal haemorrhage on the posterior aspect of the cerebellar hemispheres and around the left vena terminalis

14) Male, seventh child, second twin Uncomplicated delivery of 5 hrs duration, 10 days before term Lived 3 days 1 hr, 15 min, asphyxiated intermittently during the last 28 hrs Perfusion 2 hrs post mortem Autopsy No definite pathological findings Brain W 300 g Macroscopically no pathological findings

16) Male, second child, term unknown to mother Birth unexpected during vacation trip in the country A midwife called in time to accept the placenta Child quickly hospitalized due to cyanosis Mongoloid features observed on admittance W 1470 g, L 39 cm The first two days in hospital free respiration when oxygen was administered, later cyanosis and a strained respiration developed Bilirubin (serum) 14 2 mg/100 ml on the 4th day, and blood exchange transfusions were performed Systolic murmur heard over the heart Lived 16 days, asphyxiated intermittently for the last 14 days Perfused 3 hrs post mortem Autopsy Atelectasis of the lungs otherwise no pathological findings Brain W 176 g No haemorrhage, no icteric staining

17) Female second child mother neurosis and pyelitis during pregnancy, antibiotic treatment Small haemorrhage in the 6th month of the pregnancy, hospitalized Uncomplicated delivery of 5 hrs duration 2 months and 18 days premature Breech presentation W 1610 g L 40 cm Lived 10 hrs 30 min asphyxiated all the time Perfusion 1 hr, 40 min post mortem Autopsy Atelectasis of the lungs which were sinking in water Brain W 170 g Smaller subarachnoidal haemorrhages around the brain stem and over the cerebral hemispheres

18) Male, no information about the family, except the mother being Rh pos Uncomplicated delivery lasting only one hour One month, 11 days premature W 1850 g L 42 cm Normal respiration the first day, later respiratory distress with a severe cyanosis, and a slight icteric staining of the skin developed Penicillin Streptomycin administered on account of crepitation heard over the lungs Dosage not mentioned The last day sanguineous froth around the mouth, [illegible]

19) Male, second child, uncomplicated delivery during transportation to hospital Respiratory distress with cyanosis developed immediately W 1750 g L 42 cm Breech presentation [illegible]

20) Female first born placental bleeding 2 months before term, caesarean section, Pentothal-Curacit narcosis W 1500 g L 40 cm. The child cyanotic cried weakly Asphyxia and cyanosis continuously all of its lifetime 1 day, 8 hrs, 5 min Perfusion 2 hrs post mortem Autopsy No pathological findings Brain A blood clot the size of a pea in the cisterna magna The ventricular system filled with blood Otherwise no pathological findings

21) Male, first born 2 days overdue, duration of delivery 9 hrs W 2900 g L 49 cm Normal development until 2 days postna[illegible] 14 hrs 50 min, asphyxiated app[illegible] Haemorrhagia pulm Brain W [illegible]

22) Female fourth child, ninth pregnancy No information about conditions during pregnancy, but due to bleeding from a placenta praevia a caesarean section was performed about 14 days before term Anaesthetic Citopan 0 2 g, Curacit 50 mg W 1530 g L 42 cm [illegible] at once, and had no respiratory trouble before 5 hrs postnatally when attacks of asphyxia started In addition to the standard treatment Cardiazol and Pentazol were also [illegible] Lived 12 hrs, 6 min, asphyxiated for the last 7½ hrs Perfusion 1 hr post mortem A[illegible] Atelectasis of the lungs Brain W 200 g No abnormalities macroscopically visible

23) Male second child After a fall, labour and haemorrhage started and birth took place [illegible] 28 days before term W 1600 g L 41 cm. Cried immediately but became asphyxic after about an hr Lived 1 day 14 hrs 4 min, asphyctic for about 1 day, 7 10 hrs Perfusion 2 hrs post mortem. Autopsy Numerous small haemorrhages found in the pericardium the lungs atelectatic, sinking in water Brain W 225 g No macroscopically visible abnormalities

24) Male second child mother also one abortion During the pregnancy small [illegible] at about mid term otherwise normal conditions Term not exactly known After 4 [illegible] labour, a macerated foetus of 6 0 g was delivered, and a twin male W [illegible] [illegible]

Autopsy Low content of air in the lungs which sank in water Brain W 2[illegible] g [illegible] scopic pathological findings No icteric staining

26) Male second child delivered 1 month 11 days prematurely W 2130 g L 41 5 cm The child cyanotic with feeble cries and a strained respiration [illegible] Spinal puncture Haemorrhagic spinal fluid Lived 1 day 8 hrs, asphyctic all the time Perfusion 1 hr 40 min

post mortem Autopsy Lungs highly congested Brain W 180 g Some coagulated blood in the cerebellomedullary cisterna Slight icteric staining of the spinal fluid

27) Female, first child, first pregnancy Mother Rh neg, father Rh pos No Rh antibodies found in the blood of the mother 1 month, 11 days before birth Delivery 11 days overdue, first cry 5–6 minutes after birth W 2920 g L 49 cm Asphyctic Spinal puncture Yellow staining of the liquor Serum concentration of bilirubin 2 days before mors 1 2 mg/100 ml Lived 1 day, 18 hrs, 30 min, asphyctic all the time Perfused 2 hrs post mortem Autopsy Vit org cordis, persistent vena cava sup sin and a septal defect Brain W 340 g Subpial haemorrhage bilaterally around the central sulcus and on the tentorial surface of the occipital lobe

28) Male, first born, 2 months and 12 days premature W 1360 g, L 39 5 cm The child cyanotic, cried feebly, respiration sounds weak Lived 1 day, 9 hrs, and 5 min, asphyxiated for 1 day, 2–6 hrs Perfusion 2 hrs post mortem Autopsy not performed Brain W 147 g Icteric staining of the walls of the ventriculus septi pellucidi No haemorrhage

29) Male, first born, birth 5 days after estimated term, some haemorrhage the last days of pregnancy W 2380 g, L 46 cm Pitocin i v administered during birth, due to weak labour The child relaxed, cyanotic, did not cry at once Later constant respiratory distress Moro reflex negative Lived 15 hrs, 10 min, asphyxiated all the time Perfusion 1¾ hrs post mortem Autopsy No pathological findings Brain W 360 g No pathological findings macroscopically

30) Male, third child, mother also one abortion 5 years earlier During this pregnancy a haemorrhage occurred in the 4th month, when Pitocin was given, seemingly without effect, as slight bleeding continued The movements of the foetus became weaker Birth 1 month and 17 days premature, birth duration only a few hrs W 1890 g, L 42 cm The child cyanotic, hypotonic, no cries no movements Moro reflex negative Weak respiration Lived only 4½ hrs Perfusion not permitted, but the corpse placed in the refrigerated room and autopsy performed the next morning Autopsy Extensive atelectasis of the lungs Brain W 220 g The gyri not fully developed otherwise no pathological findings

32) Male second child, 2½ months premature, foot presentation Birth duration 2½ hrs W 1450 g L 41 cm The child cyanotic, feeble cries, but the condition improved after 10 min Later again respiratory distress, lived 7 hrs 20 min Asphyxiated for about 5–6 hrs Perfusion not permitted and autopsy not performed The corpse placed in the refrigerator and the brain removed the next morning Brain A considerable haemorrhage around the brain stem the ventricular system filled with blood clots Otherwise no pathological findings

33) Female second child Rhesus status not given Birth 2 months, 6 days before term, lasting for only 1 hr, 35 min The child cyanotic. W 1120 g L 36 5 cm Respiratory distress some tonic convulsions, auscultatory crepitation Lived 11 hrs, 10 min, asphyxiated all the time Perfusion and autopsy not performed The body placed in the refrigerator, the brain removed about 8 hrs later No macroscopically visible pathological changes in the brain

35) Female second child About 1½ months before term some haemorrhage occurred, and labour started Birth within a few hrs W 2120 g L 44 cm Cried after aspiration, but was cyanotic and had respiratory distress Some haemorrhagic mucus around the mouth and increasing cyanosis when crying Lived 1 day 11 hrs, 25 min, asphyctic all the time Perfusion 2 hrs post mortem Autopsy No pathological findings Brain W 275 g No pathological findings macroscopically

38) Female birth on term W 4000 g 14 days after birth the mother developed mastitis and was hospitalized the child developed a phlegmonous sublingual abscess Due to dyspnoea and

vulsions and apnoeic periods occurred, increasing in length and severity Lifetime 3 days, 50 min, asphyctic for 8–12 hrs Perfusion 2 hrs post mortem Autopsy Normal findings Brain W 342 g The gyri somewhat flattened, and the ventricles narrow, otherwise no pathological findings

Cases excluded from the material

For various reasons, twelve of the original 60 cases are omitted from the material In the cases 1, 8, 9, and 36, the cut separating the medulla from the spinal cord passed through the lower part of the cochlear nuclei, thus rendering them unsuitable for a reliable counting

6) This brain was accidentally destroyed

13) Female, first born, spontaneous delivery 1 month, 6 days premature W 2450 g, L 45 cm Lived 2 days, 52 min, asphyxiated 1 day, 2–3 hrs Perfusion 4 hrs, 20 min post mortem Autopsy No pathological findings Brain Haemorrhage around the cerebellum By accident a part of the dorsal nucleus was cut away The ventral nucleus contained 38,100 cells

25) In this case the cochlear nuclei were cut in sagittal sections owing to an error, and it was considered unsuitable for comparison

37) Male, 34 years died of an acute heart infarction This was at first considered a case suitable for the control group, as none or a very short asphyxiation period was involved The cochlear nuclei contained 83,700 cells However, when the full case history was obtained, it turned out that the patient had suffered from cerebral commotions three times and a grinding murmur had been heard over his heart for some time For these reasons, the case was excluded from the material

44) Female, 8 years, died of acute nephritis This case was also thought fitted for the control group especially as an audiogram, taken after adenotomy three months before death showed normal hearing However, as she had been uraemic for 1½ months before death with spasms, convulsions and encephalopathia the case was rejected Countings were performed, however, and the cochlear nuclei contained 98 800 cells the dorsal nucleus 18 200 cells

45) Male, 8 years, killed in a traffic accident Also a case selected for the control group, but it was learned that he had suffered from commotio cerebri twice before, and that he was comatose for 6 hrs before death Countings were performed, however, and his cochlear nuclei contained 70 100 cells, the dorsal nucleus 17 000 cells An audiogram performed at school 10 months before death showed a hearing threshold of 15 Db for all the usual frequencies

50) Female, first born second pregnancy A caesarean section performed approximately 2 months and 8 days before term, on account of a threatening eclampsia Cried at once, regular respiration W 800 g, L 34 cm 3 weeks old, vomiting and diarrhoea Staphylococcus aureus isolated from the faeces Bacimycin treatment initiated This was given perorally, and was diluted in saline, which possibly led to oedema of the brain, convulsions and asphyxia Lived 1 month, asphyxiated for the last two days Perfusion 1½ hrs post mortem Autopsy not performed Brain W 207 g No pathological findings Countings Cochlear nuclei 59,200 cells dorsal nucleus 10 900 cells

56) Female, first child, mother in a toxic condition for the last month of the pregnancy, with hypertension and albuminuria Caesarean section performed 9 days before term Condition not

irregular respiration, sharp 'cerebral' cries The skin grey cyanotic Spinal puncture showed haemorrhagic liquor yellow stained after centrifugation Lifetime 1 day, 9 hrs, 55 min, asphyxiated for the last 6½ hrs Perfusion 1 hr, 10 min post mortem Autopsy Brain W 320 g Haemorrhage found around the brain stem, along the sulci on the convexity and in the ventricular system

49) Female, first child the mother had a urinary infection at the beginning of the pregnancy, and a general exanthema of the skin when admitted for delivery 6 hrs before birth 1cc of morphine i m Birth 10 weeks premature W 1090 g L 37 5 cm Several fresh infarctions found in the placenta The child cried at once, but was cyanotic without additional oxygen administration After the first 12 hrs the condition improved Glucose-bicarbonate administered for 3 days Colour and general condition normal until the 10th day of life Then the situation suddenly changed On the suspicion of aspiration suction was performed by an anaesthetist The last day of life artificial respiration several times Lived 10 days, 19 hrs, 5 min, asphyxiated 1 day, 10 hrs Perfusion 2½ hrs post mortem Autopsy Extensive atelectasis in the lungs No indications of aspiration or bronchopneumonia Brain W 145 g The left cerebral hemisphere a little larger than the right one, otherwise no pathological findings

52) Male, third child Born about 3 months before term, birth lasting 11 hrs, 15 min The mother had lost the amniotic fluid 14 days before W 1100 g L 36 cm Cyanotic child but its cries were strong Antibiotics on account of crepitation heard over the lungs, penicillin, 50 000 I U for 6 days and streptomycin, 40 mg for two days, and 25 mg for the next four days Lived 5 days, 12 hrs, 45 min, asphyxiated for approximately 3½ days Perfusion 2½ hrs post mortem Autopsy not performed Brain W 141 g The left hemisphere was a little larger than the right one, otherwise no pathological findings

53) Female, first child, mother one earlier abortion in the 6th month of pregnancy About 2¾ months premature Cyanotic, feeble cries W 1070 g, L 36 cm A somewhat better condition during the first hrs no cyanosis when oxygen supplied, but later respiratory distress followed by cyanosis, refractory to stimulation Lifetime 1 day, 14 hrs, 15 min Asphyxiated for approximately 1 day, 10 hrs Perfusion 1 hr, 40 min post mortem Autopsy not performed Brain W 140 g Subarachnoidal haemorrhage on the basis cerebri and two smaller haemorrhages, the size of peas located on the left side in the centrum semiovale, on the right side between the posterior and inferior horns of the lateral ventricle

54) Male, second twin, mother s fourth birth Born three quarters of an hour after the first twin (No 55) About 1–1½ months premature Due to a transverse position, this twin was manually turned, and a foot extracted Type of narcosis not mentioned, but the child was weak cried only after bathing, received 20 mg Lobellin W 1750 g, L 42 cm Gasping respiration, which continued for the first hr, but improved after mouth to mouth respiration After a few hrs respiration stopped Lifetime 4 hrs 18 min, asphyxiated all the time Perfusion 1 hr, 40 min post mortem Autopsy The lungs partly atelectatic No bronchopneumonia no hyaline membranes Brain W 250 g No pathological findings macroscopically

55) Male twin to No 54 W 1800 g, L 41 cm Cried immediately after birth but had a superficial irregular respiration and the cries were feeble The following day, however the condition had improved and no oxygen administration was needed The next day again cyanotic, crepitation heard over the lungs Penicillin-Streptomycin and Acylanid for digitalization were given Lived 1 day, 18 hrs 30 min asphyxiated for 11–20 hrs Autopsy not performed Brain W 247 g No pathological findings

58) Male first born normal birth 3 days overdue The amniotic fluid however was greenish and thick W 1810 g L 45 cm Suction and artificial respiration for two minutes before the child cried Somewhat feeble the first day but more vital the next 1½ days old fits of con-

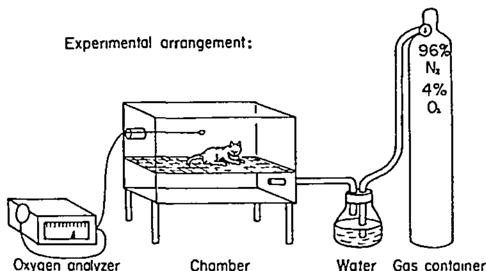


Fig 2

ated kitten of the same litter was sacrificed The others, with a few exceptions to be described later, were given a gas mixture of 96% N_2 and 4% O_2 in the following way

The kittens were placed in an airtight container, with an inlet opening for a gas tube of 6 mm internal diameter, and an outlet with a diameter of 33 mm, to secure an outlet for the pressure The gas mixture from the container passed through a flask of water, chiefly in order to see the amount of gas passing the water (Fig 2)

After a brief flushing, a 4% oxygen content was attained in the container, and maintained by a constant flow

In our laboratory the O_2 content of the containers was controlled with a Beckman oxygen Analyzer, model D 2 This analyzer operates on the principle that oxygen is strongly attracted into a magnetic field Our analyzer had a scale graduation of 0-20%

The experiments proved that a gas mixture containing 4% oxygen was endured for some time, whereas 3% usually led to a quick respiratory failure One litter of kittens Nos 12, 13, 14 and 15, on their 5th day of life were exposed to a 3% O_2 mixture for a quarter of an hour, because at that time no other mixture was available This litter did not tolerate the 3% mixture for more than a quarter of an hour, when signs of respiratory failure occurred However, one kitten (No 1) endured the 3% mixture for 10 hours

In the first litter of kittens (Nos 1, 2, 3), 1 5%, 3%, 4% and 9% oxygen were tried The 4% mixture seemed to be the lowest the kittens could endure for some time Of course there were individual variations, and also the age of the kittens seemed to be a factor of importance the younger the kitten, the better, apparently, was the asphyxia tolerated

Once each day the kittens were put into the chamber, and kept there until respiration became superficial and nearly stopped Their noses, ear-tips and paws

known for the first two days the last day pale grey cyanotic some convulsions at first later tonic spasms Lived 3 days 9 hrs 10 min Perfusion 2 hrs post mortem Autopsy not performed Brain W 340 g No pathological findings Countings Cochlear nuclei (0 100 cells dorsal nucleus 10 500 cells

The experimental material

The finding of a severe loss of nerve cells in the cochlear nuclei prompted the question whether the same cell loss might also be produced experimentally, under conditions similar to the human neonatal asphyxia, i e periodical sublethal attacks of severe hypoxia until death occurred from hours to some days postnatally The first step in this program would evidently be the determination of the number of cells normally found in the cochlear nuclei of kittens By choosing kittens of different ages, one would also be able to determine whether in kittens a postnatal increase in the number of nerve cells takes place Kittens were chosen as experimental animals because they were easily available The use of kittens offered several advantages their date of birth is usually known, and thus their exact age Their auditory organs are much like the human, the hearing of a cat being perhaps a little better than ours

The chance of birth trauma is negligible, and if kept and fed by the mother, any loss of cells in their cochlear nuclei, or degenerations in their cochleae would in all probability result from the experimental hypoxia

The conditions of new-born human babies suffering from asphyxia cannot be exactly copied experimentally, especially as our knowledge of all the factors involved is far from complete But at least the most important factor, the lack of oxygen may be introduced in the experiments If the brains of the kittens are fixed intravitally, the autolytic changes so often met with in human preparations may be wholly avoided

Normal kittens

Twenty six kittens of 6 different litters were used

Six died during the experiments and were discarded The remaining 20 belonged to 5 different litters They were all fed by their mothers until the time of sacrifice Anaesthesia was induced by Nembutal intraperitoneally 0 5 ml/kg, followed by perfusion with saline, and then with the Heidenhain-Susa solution as described for the human brains The medulla oblongata was removed, embedded in paraffin sectioned and stained as previously described Every 10th section was mounted and the nerve cells of the cochlear nuclei counted

Asphyxiated kittens

Six litters with in all 29 kittens were used in these experiments One kitten of each litter served as a further control, in addition to the 26 normal kittens earlier described The control material was spared until the day the last asphyxi-

22-hour-old kitten which died after breathing the 4% mixture for a period of 6 hours

These three were fixed immediately after death to be included in the material, even if a visible influence on the nerve cells of the cochlear nuclei might be suspected only in the first one The fourth (No 15), however, died in the cage with its mother at the beginning of the night after an asphyxiation period, and was not found before the next day, after approximately 12 hours This animal was discarded

This leaves a series of 22 asphyxiated kittens, and 6 (+ 26) controls

The respiration was also a good sign of the tolerance of anoxia At the start of an experiment the respiration rate per minute usually rose to about 80 or more After the first half hour the rate declined to about 40/minute If the respiration rate stayed between 20–40 for the next hour, the kitten could endure a continued exposure, but if the animal started gasping, a sudden respiration stop could be expected, and the kitten had to be taken out and given artificial respiration During the procedure every kitten had to be resuscitated (sooner or later) Either a thoracal intermittent pressure or mouth to mouth respiration usually restored gasping, which, after some minutes in the open air became a regular, though slow, respiration Thus, every one of the experimental kittens, like the asphyxiated babies, was on the brink of death once or more often during the experimental period

After their daily period of asphyxiation, the animals were left with their mother All of them showed abnormal behaviour Reduced suction ability, a restless and uneasy sleep, ataxic movements of the head when trying to reach the papilla mammae, crawling in circles, etc Some were sleeping lying straight on their backs with the paws in the air, a posture very seldom seen in cats

To allow time for the manifestation of potential pathological changes, the kittens were left with their mother from 1 to 4 days before they were sacrificed The three kittens that died during the experiment were fixed immediately by perfusion Two of the others were sacrificed one day after their last asphyxiation period, four after two days, seven after three days, and six after four days Bearing in mind that several of the human babies with a life-span of only 10–20 hours, displayed very definite pathological changes, the post-asphyxiation time in these kittens should suffice for signs of degeneration or cell losses to occur

After perfusion of the head, the part of the medulla oblongata containing the nuclei was removed, and prepared as described In all the asphyxiated kittens the cochlea was also removed for histological examination, in the first three animals bilaterally, in the rest on one side only

The first three showed that a preparation containing both the cochlea and the cochlear nuclei on the same side was not suitable for the purpose A cell count in the nuclei demanded thionine staining, which was not very successful if the preparation also had to be decalcinated Then the cell borders became blurred, and the whole nuclei too homogeneous for counting Therefore, in the following specimens the preparation was cut sagittally in the median plane, and one side was used for the cochlear preparations, haematoxylin eosin stained, and the other for the counting of nerve cells, thionine-stained

were then quite white, a sign of deficient circulation The new-born and 1–3-day-old kittens could stand asphyxia up to 6 hours, but those one and two weeks or older usually did not endure the oxygen deficient atmosphere for more than an hour at a time (Table 2)

TABLE 2 Distribution of the asphyxiation periods

No	Age at start	Asphyxiation period per day						Total
		1	2	3	4	5	6	
1	0d	1h 9%	2h 3%	4h 3%	4h 3%			10h 3% 1h 9%
2	7d	2h	3h	5h 30m	5h			15h 30m 4%
3*	14d	5h	5h + some m 1½°					10h 4% + some m 1½%
4*	12d	45m						45m 4%
5	12d	45m	35m	40m	20m	25m	35m	3h 20m 4%
6	12d	45m	35m	40m	30m	45m	40m	3h 55m 4%
7	12d	45m	35m	40m	30m	45m	45m	4h 4%
8	12d	45m	35m	40m	30m	45m	45m	4h 4%
9	7d	45m	35m	40m	30m	1h	1h 45m	5h 15m 4%
10	7d	45m	35m	40m	30m	1h	1h 45m	5h 15m 4%
11	7d	45m	35m	40m	30m	1h	1h 45m	5h 15m 4%
12	3d	1h 40m	15m 3%	3h	3h	3h		10h 40m 4% + 15m 3%
13	3d	1h 40m	15m 3%	3h	2h 30m	1h		8h 10m 4% + 15m 3%
14	3d	1h 40m	15m 3%	45m	30m	1h		3h 55m 4% + 15m 3%
15*	3d	1h 40m	15m 3%	3h	3h	1h		8h 40m 4% + 15m 3%
16	¾d	4h 30m						4h 30m 4%
17	¾d	6h						6h 4%
18*	¾d	6h						6h 4%
19	¾d	4h						4h 4%
20	0d	3h						3h 4%
21	0d	3h						3h 4%
22	0d	3h	3h 30m		4h	5h	3h 15m	18h 45m 4%
23	1d	3h 30m		4h	5h	3h 15m	2h	17h 45m 4%

h = hours m = minutes d = days * = died during experiment

A 4% oxygen mixture was used in all experiments except in those where another mixture is specifically mentioned

Four kittens died during the procedure One (No 3) died at 16 days old after two periods of 5 hours in the 4% mixture, and later some minutes in a 1½% mixture which was accidentally used The second (No 4) died at 12 days old after only three quarters of an hour in the 4% mixture The third (No 18) was a

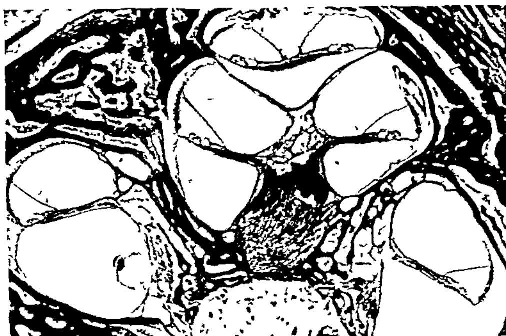


Fig 3 Section through human cochlea Control case No 51 Haematoxylin-eosin stain × 25

The basilar membrane consists of connective tissue and radially arranged basilar fibres, forming a single layer in the arcuate zone and a double layer in the pectinate zone Axially the basilar membrane is attached to the tympanic lip of the osseous spiral lamina, laterally to the spiral ligament

The organ of Corti consists of supporting cells, sensory cells and nerve fibres with nerve endings The characteristic framework of the supporting elements and sensory cells also includes several regions containing the fluid inside the organ of Corti These are the inner and outer tunnels, the space of Nuel and the spaces around the sensory cells (Engstrom *et al* 1964) The sensory elements form one row of inner, and three, sometimes four and even five rows of outer hair cells. The appearance of these cells is a good indicator of the quality of the preparation The outer hair cells are cylinder-shaped, their nuclei round and situated in the basal portion of the cell The inner hair cells are bottle shaped, their round nuclei situated in the lower, wider part of the cell

Above the organ of Corti the fibrous and gelatinous tectorial membrane rests on the Hensen cells and the hairs of the sensory cells It is axially attached to the vestibular lip

With high power the finer structures of the cells may be recognized Each hair cell, on its upper free surface is provided with a cuticular plate from which a large number of stereocilia or hairs protrude towards the tectorial membrane Below the cuticular plate of the outer hair cells an aggregate of mitochondria and lamellae is found, some of these form the Hensen body In the infranuclear region large clusters of mitochondria form the body of Retzius

Premature kittens

A litter of 7 premature kittens delivered by caesarean section was also examined, for two different purposes to observe the reaction of the cells in the cochlear nuclei of premature kittens to asphyxia, and to establish whether there were any differences in the number of nerve cells in premature as compared to full term kittens

The greatest difficulty in this connection was to ascertain the exact date of conception In freedom one would never get the exact date However, the act was observed when two recently imprisoned cats were brought together

The female was transferred to a separate cage, and kept there till the 56th day of the gestation period, which in cats averages 63 days (Spector 1956) A caesarean section was then performed Nembutal was chosen as the anaesthetic because ether usually produces increased mucous secretion, and nitrous oxide anaesthesia is difficult to maintain for some time and has a very small margin However, as it turned out the seven kittens of this litter were highly asphyctic when delivered Whether this was due to their prematurity or to the anaesthetic cannot be ascertained

Of the seven premature kittens, three died after a few minutes Their only breathing amounted to a few gasps, and artificial respiration failed

Numbers 4, 5, and 6 lived for 3½, 6, and 7½ hours, were asphyctic throughout, and had to be given mouth to mouth respiration at intervals A part of the plan was to give a couple of these premature kittens an exposure to the low-oxygen chamber, for comparison with their siblings Only in one kitten, however, could the plan be carried out fairly successfully The animal survived through the first day, though asphyctic at intervals, and on the next day endured a stay in the chamber for 2½ hours The third day it would not swallow and was given saline subcutaneously and kept warm, but it expired in the evening

OBSERVATIONS

The human material

The cochlea

Before describing the findings in the inner ear of the asphyxiated human foetuses a brief survey will be given of the structure of the cochlea, as described in the literature and revealed by the most successful preparations of the present material

At low magnification the general shape of the cochlear duct and its structural components can be easily recognized

In an axial section the cochlear duct is triangular, bordered laterally by the stria vascularis upwards by the vestibular membrane and downwards by the basilar membrane on which rests the organ of Corti (Fig 3)

and seldom more than one, distinctly visible nucleolus They are rich in a fine, evenly distributed Nissl substance, which, however, is not so easily recognized in a haematoxylin eosin stained preparation

Usually the afferent olivo-cochlear bundle can be recognized inside the spiral ganglion

An excellent survey of the normal picture of the organ of Corti has been given by Retzius (1884) and by Bloom and Fawcett (1962) In recent years, the ultrastructure of the various elements of the organ of Corti has also been studied by electron-microscopy (e g Engstrom *et al* 1964)

Description of cases

Control case

51 Right side

The organ of Corti is well preserved The inner and outer hair cells are normal The vestibular membrane is straight The tectorial membrane contacts the surface of the organ of Corti In the stria vascularis the thin layer of cubical cells can be distinguished on the surface The ganglion cells are normal

Left side

This preparation has not been so successful as that of the right side The hair cells look normal, but the papilla basilaris is low, the pillar cells bent, and the spiral ligament is detached from the bony wall The cytoplasm of the ganglion cells shows some shrinkage

Asphyxiated cases

16 Right and left sides

The organ of Corti is somewhat compressed, the pillar cells are bent Both inner and outer hair cells are present Of the border cells and the inner phalangeal cells only the nucleus is visible Some of the cells of the spiral ganglion contain vacuoles and their cytoplasm is indistinct

17 Right and left sides

Some compression of the organ of Corti, including the vestibular membrane, which in some places is adhering to the tectorial membrane The contours of the Hensen cells are indistinct, the papilla basilaris is low The pillar cells are bent, the stria vascularis flattened However, both inner and outer hair cells are intact, and the fluid spaces within the organ of Corti are present The cells of the spiral ganglion have a normal appearance

19 Right and left sides

Some compression of the organ of Corti, mostly on the right side The spiral ligament is detached from the bony wall, the vestibular membrane wavy, in some places broken The stria vascularis is well preserved, on the right side, however,

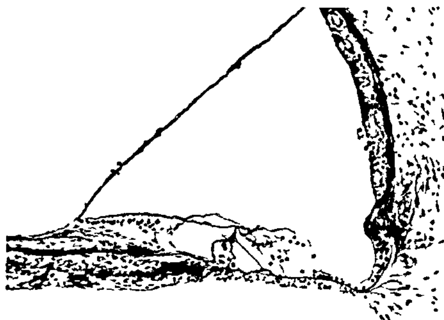


Fig 4 Basal coil of cochlea from Fig 3 × 150 The folding of the cuticular plate is an artifact, the organ of Corti appears normal

The basal ends of the hair cells are surrounded by groups of nerve endings which are visible in successfully stained haematoxylin eosin sections

The inner tunnel is formed by the inner and outer pillar cells which are resting on the basilar membrane (Fig 4)

The pillar cells contain large numbers of tonofibrils which spread out fan-wise in both ends of the pillars The round nuclei surrounded by cytoplasm occupy the basal part of the pillar cells The pillars rest on and cover the basilar membrane The outer phalangeal cells of Deiters are situated beneath the outer hair cells Their nuclei form an uneven row in the basal parts of the cells close to the lower ends of the sensory cells In successful preparations their phalangeal extensions may also be recognized Lateral to the outer hair cells the cells of Hensen constitute the most prominent part of the papilla basilaris The cells are arranged in several rows, their height decreasing rapidly in a peripheral direction The nuclei are round in the basal coil more oval towards the apex of the cochlea A high convex and even curve formed by these cells is a valuable indication of a successful fixation as are straight basilar and vestibular membranes

The stria vascularis has a low irregular columnar epithelium with cellular extensions close to the walls of the numerous capillaries The spiral prominence is seen above the outer sulcus (Fig 4) At high power the fibres of the cochlear nerve may be recognized below the hair cells They cross the inner tunnel, penetrate the basilar membrane and run through the canals of the spiral osseous lamina to the spiral ganglion in the modiolus The bipolar cells of the spiral ganglion form clusters or groups separated by nerve fibres, connective tissue and vessels They are round or oval and contain a large, round, centrally placed nucleus

However, both inner and outer hair cells look normal, the nerve fibres to the organ of Corti and the cells of the spiral ganglion are well preserved

26 Right side

This is the first preparation in which the Heidenhain Susa fluid was used for perfusion

There is a marked difference, especially in the organ of Corti The papilla basilaris is higher, and in the normal looking hair cells intracellular structures like the bodies of Hensen and of Retzius may be recognized The stria vascularis has a normal appearance, but its vessels are filled with blood, indicating a failure in the perfusion The cells of the spiral ganglion look normal in the apical regions, and smaller, with a somewhat shrunken cytoplasm basally in the modiolus

Left side

The findings are comparable to those on the right side, but there is a pronounced compression of the organ of Corti A pink coloured substance fills the scala tympani The basilar membrane bulges upwards in all coils Blood is seen in the inner meatus

27 Right and left sides

The papilla basilaris is high, the hair cells and the Hensen cells are straight, but in some places the pillar cells are slightly S shaped In these regions also the vestibular membrane is wavy and the vestibular ligament detached from the bony wall The hair cells the stria vascularis, and the ganglion cells all look normal

28 Right and left sides

A preparation, showing a normal organ of Corti, well preserved stria vascularis, and no pathological changes in the cells of the spiral ganglion (Fig 5)

29 Right and left sides

The surface layer of cuboidal cells in the stria vascularis is exfoliated, and the cells partly scattered as debris in the cochlear duct The spiral ligament is detached from the bony wall, and on the left side the basilar membrane is broken in the basal coil However, the preparation of the organ of Corti is successful, permitting a detailed study of the hair cells and supporting elements

The nerve fibres and the cells of the spiral ganglion appear normal

35 Right and left sides

Areas of vacuolization are seen around the inner hair cells, otherwise a successful preparation The outer hair cells are cylindrical, their nuclei are round and of normal size The nerve contacts around the bases of the outer hair cells are seen, and the nerve fibres can be followed through the tunnel of Corti to the apparently normal ganglion cells The stria vascularis is well preserved in every coil, and its cells are distinct and well stained

the nuclei of its cells are in some places pycnotic Both inner and outer hair cells are seen fully developed, and in the supporting structures the main configuration is recognized The cells of the spiral ganglion look normal

20 Right side
The supporting structures in the organ of Corti are compressed, but are present to a normal extent The stria vascularis shows compression of its vessels, a flattened epithelium and pycnotic nuclei Inner and outer hair cells look normal The spiral ganglion is well preserved, but the nuclei of the nerve cells are a little shrunken

Left side
Some compression, especially of the stria vascularis, and the cytoplasm of the inner hair cells and the border cells is shrunken Otherwise no irregularities are found, the outer hair cells look normal, as do the cells of the spiral ganglion

21 Right side
The basilar membrane is torn in some places in the basal coil The spiral ligament is detached from the bony wall However, the hair cells are present, and no major cell destructions are seen The cells of the spiral ganglion show some shrinkage of their cytoplasm, but their nuclei are normal

Left side
The stria vascularis is remarkably flat, and in the cells of the spiral ganglion the same shrinkage of the cytoplasm is seen as on the right side However, both inner and outer hair cells are present, and the main features of the organ of Corti are recognized in all coils The limbus and the papilla basilaris are low

22 Right side
The organ of Corti is not well preserved in this case It is possible to see both inner and outer hair cells, and the supporting cells are present Their nuclei are distinct, but their cytoplasm is shrunken with indistinct borders Some compression of the organ of Corti is seen The stria vascularis and the cells of the spiral ganglion look normal

Left side
On this side also the organ of Corti is compressed, but the fixation has been more successful The different details in the organ of Corti can be better observed The hair cells look normal, and well-preserved supporting cells are present No signs of degeneration are found in the stria vascularis or in the spiral ganglion

23 Left side
The spiral ligament is detached from the bony wall in the middle and apical coils Some compression of the organ of Corti is present The tectorial membrane is thin, collapsed over the organ of Corti The stria vascularis is flattened

40 Right and left sides

Some blood is seen in the perilymphatic spaces The organ of Corti is well preserved, both inner and outer hair cells look normal The papilla basilaris is high, in the stria vascularis and the ganglion cells normal features are found The vestibular membrane is curved towards the limbus

41 Right side

The vessels are filled with blood, indicating unsuccessful perfusion Blood is also found in the perilymphatic spaces The spiral ligament is detached from the bony wall, and the vestibular membrane is curved into the cochlear duct In the basal coil the long, cylindrical form of the hair cells is recognizable, their borders and the protruding hairs are distinct In the middle and apical coils the borders of the hair cells are indistinct, the cytoplasm homogeneous and their upper region and the reticular membrane are without distinction Vacuolization is seen in the region of the inner hair cells The cytoplasm of the spiral ganglion cells is shrunken, but their nuclei look normal

Left side

On this side less blood is found in the vessels, but precipitates and globular formation are seen over the organ of Corti Otherwise the findings are similar to those on the right side

42 Right side

Some blood is present in the perilymphatic spaces, but the organ of Corti, the stria vascularis, and the spiral ganglion all look normal

Left side

Some shrinkage and vacuolization of the cytoplasm are found in the area of the inner hair cells and the vestibular membrane is curved towards the cochlear duct Otherwise the preparation looks normal

43 Right and left sides

The organ of Corti the stria vascularis and the ganglion cells all look normal

47 Right side

A pink coloured substance fills the perilymphatic spaces Some of the cells in the spiral ganglion show a shrinkage of the cytoplasm The structure of the organ of Corti is preserved and the hair cells are normal The vestibular membrane is depressed towards the tectorial membrane Normal findings in the stria vascularis

Left side

The vestibular membrane wavy, the basilar membrane is bent in the area of the pillar cells Outer and inner hair cells, the stria vascularis and the spiral ganglion look normal

48 Right and left sides
Successful fixation has preserved the structure of the organ of Corti, even the inner hair cells, very well, but blood is found in the perivascular spaces

49 Right and left sides
In the middle and apical coils the limbus is low, and the vestibular membrane touches the limbus and the tectorial membrane The cytoplasm of the inner hair cells is poorly stained and vacuolized However, in the basal coil they appear normal The cells of the spiral ganglion and the stria vascularis look normal in all coils

52 Right side
The vessels are filled with blood In the middle and apical coils the vestibular membrane touches the limbus, but in the basal coil it is free In the basal coil the basilar membrane is bent in the zona pectinata
The hair cells are well preserved, and the limbus is high, but the papilla basilaris is low In the apical region the cells of the spiral ganglion look normal, but basally some cells contain vacuoles and have pycnotic nuclei

Left side
In the upper coils, the organ of Corti is compressed, with flattened stria vascularis and the vestibular membrane lying immediately over the limbus In the basal coil, globular formation is seen over the organ of Corti and on the stria vascularis The cytoplasm of the hair cells is shrunken, their nuclei darkly stained However, this picture is not found throughout the cochlea, in some parts the structure and the arrangement of the cells of the organ of Corti are normal

53 Right and left sides
The organ of Corti appears normal with distinct inner and outer hair cells and well preserved supporting elements The cells of the spiral ganglion look normal

54 Right and left sides
In this case the fixation of the labyrinth has been very good, no pathological changes are found within the organ of Corti or in the adjacent structures (Fig 6)

55 Right and left sides
Some blood corpuscles are seen in the scala vestibuli in the basal regions of the cochlea otherwise all the features of the organ of Corti, the stria vascularis, and the spiral ganglion are normal

58 Right and left sides
In the region of the inner hair cells space formation and vacuolization are seen The cytoplasm of the inner hair cells, the border cells, and the inner phalangeal cells is shrunken the nuclei are pycnotic Some pycnotic nuclei are also seen

in the spiral ganglion Globular formation is present at the edge of the stria vascularis The vestibular membrane is wavy However, the organ of Corti is in other respects well preserved, the outer hair cells look normal, the papilla basilaris is high, and the supporting cells do not show any obvious changes

The cochlear nuclei

The cochlear nuclei in man constitute a spindle shaped complex (Fig 7) Its rostral end is formed by the ventral nucleus, its caudal end by the dorsal

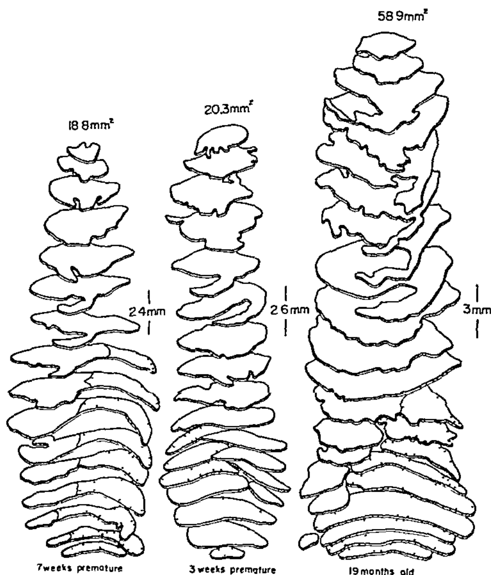


Fig 7 Drawings of sections of the cochlear nuclei at three stages of development Every 10th section is drawn Dorsal cochlear nucleus dotted

TABLE 3 *Average volume of the cochlear nuclei (in mm³)*

Age	No of cases	Mean volume	Standard deviation	No of cases	Mean volume	Standard deviation
	Control cases					
	Both nuclei			Dorsal nucleus		
10 years	2	10 5	1 3	2	3 1	0 0
1 10 "	4	8 8	1 0	3	2 3	0 3
< 1 "	4	5 2	0 9	4	1 5	0 6
	Asphyxiated cases					
Full term or overdue	8	3 6	1 3	8	0 9	0 4
< 1 month premature	5	3 4	0 8	5	0 9	0 1
1 2 months "	9	2 9	0 4	10	0 7	0 2
2 3 " "	11	2 8	0 4	11	0 7	0 1
3 " "	6	2 6	0 6	6	0 6	0 2

The standard deviation is calculated according to the formula

$$S = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (X_i - X)^2}$$

X — the average mm³
X_i the single volume observation
N — number of nuclei

nucleus bulging out into the lateral recess of the fourth ventricle to form the tuberculum acusticum The ventral nucleus is by far the largest its volume in the normal cases averaging 71 4 % of the total (see Table 3 and Fig 7)

In transverse sections the dorsal nucleus is sickle shaped curving around the lateral aspect of the restiform body The lateral surface of the nucleus contacts the flocculus and its peduncle (Fig 8A) The nerve cells are small, spindle shaped oval or polygonal (Fig 9A) In thionine sections the cytoplasm is frequently deeply stained The Nissl granules are fine, a little indistinct evenly distributed throughout the cytoplasm The characteristic lamination found in the dorsal cochlear nucleus of the cat is only indicated in the human dorsal cochlear nucleus (Fig 10)

The ventral nucleus is pear shaped with the tapering end pointing dorsally (Fig 8B) The acoustic nerve enters the medioventral circumference of the nucleus The cells of the ventral nucleus are spherical (Fig 9B) and larger than those of the dorsal nucleus The fine Nissl granules are evenly scattered and numerous in the cytoplasm except at its outer border which gives the cells a somewhat blurred appearance at the periphery

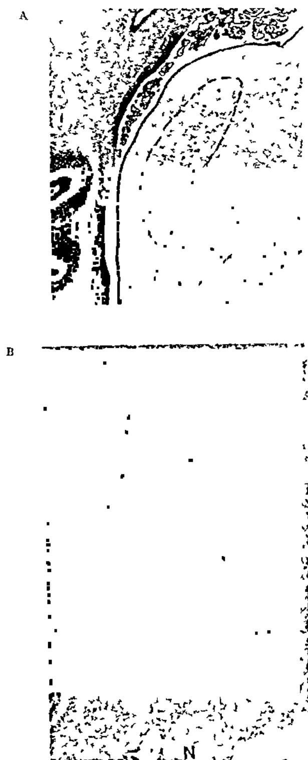


Fig 8 The cochlear nuclei A Dorsal nucleus case No 18 B Ventral nucleus case No 52 R Restiform body FI Flocculus N VIII nerve Thionine stain × 30

TABLE 3 *Average volume of the cochlear nuclei (in mm³)*

Age	Both nuclei			Dorsal nucleus		
	No of cases	Mean volume	Standard deviation	No of cases	Mean volume	Standard deviation
Control cases						
10 years	2	10.5	1.3	2	3.1	0.0
1–10 "	4	8.8	1.0	3	2.3	0.3
< 1 "	4	5.2	0.9	4	1.5	0.6
Asphyxiated cases						
Full term or overdue	8	3.6	1.3	8	0.9	0.4
< 1 month premature	5	3.4	0.8	5	0.9	0.1
1-2 months "	9	2.9	0.4	10	0.7	0.2
2-3 " "	11	2.8	0.4	11	0.7	0.1
3 " "	6	2.6	0.6	6	0.6	0.2

The standard deviation is calculated according to the formula

$$s = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(X - X_i)^2}$$

X = the average mm³
X_i = the single volume observation
N = number of nuclei

nucleus, bulging out into the lateral recess of the fourth ventricle to form the tuberculum acusticum. The ventral nucleus is by far the largest, its volume in the normal cases averaging 71.4% of the total (see Table 3 and Fig. 7).

In transverse sections the dorsal nucleus is sickle-shaped, curving around the lateral aspect of the restiform body. The lateral surface of the nucleus contacts the flocculus and its peduncle (Fig. 8A). The nerve cells are small, spindle-shaped, oval or polygonal (Fig. 9A). In thionine sections the cytoplasm is frequently deeply stained. The Nissl granules are fine, a little indistinct, evenly distributed throughout the cytoplasm. The characteristic lamination found in the dorsal cochlear nucleus of the cat is only indicated in the human dorsal cochlear nucleus (Fig. 10).

The ventral nucleus is pear-shaped, with the tapering end pointing dorsally (Fig. 8B). The acoustic nerve enters the medioventral circumference of the nucleus. The cells of the ventral nucleus are spherical (Fig. 9B) and larger than those of the dorsal nucleus. The fine Nissl granules are evenly scattered and numerous in the cytoplasm, except at its outer border, which gives the cells a somewhat blurred appearance at the periphery.



Fig 10 Dorsal cochlear nucleus and the caudal tip of the ventral nucleus
The four arrows to the left indicate the layers of the dorsal nucleus, viz a, ependymal, b, molecular, c, granular, d, middle layer The arrow e points to the border between the dorsal and the ventral nucleus, and the closely packed granular cells lateral to the ventral nucleus Thionine stain × 30.

The boundaries of the cochlear nuclei in most places are well defined in cell-stained sections, although the lateral border occasionally may appear a little indistinct, due to a diffuse scattering of neurons in the subependymal layer (Fig 11, a) Especially in the premature babies this was a common finding

Where the two nuclei are in contact, the size, form, and distribution of the cells leave little doubt with regard to the boundary between them The boundary is also pointed out by a pyramid-shaped accumulation of closely packed granular cells belonging to 'Der laterale Kornerdamm' of Fuse (1913), as appears from Figures 8 and 11

Even in the most premature cases the two cochlear nuclei were well defined, supporting the opinion of Fuse (op cit), who found that *all* elements of grey substance in an adult brain could be seen in the brain of a 5-month foetus

For computation of the volume of the nuclei their boundaries were marked by lines drawn under the projection apparatus, between the peripherally situated perikarya

Description of cases

a) The cochlear nuclei

The nerve cells of the cochlear nuclei in most cases presented a multifarious picture of changes These varied between a slight blurring of the contours of a cell to severe cell degenerations encountered in the more heavily affected cases



Fig. 11 Nucleus cochlearis dorsalis and ventralis from case 55. a, arrow points to neurons of the dorsal cochlear nucleus situated in the subependymal layer, b, arrows pointing to granular layer surrounding the ventral cochlear nucleus, c, border between the dorsal and ventral nucleus Thionine stain × 30

(Figs 12, 13). In the latter cases some cells showed disintegration of the cytoplasm, leaving as remnants of the cell a few chromatine granules around a shrunken nucleolus Between these extremities all pictures of degenerations were found, including Nissl's 'acute swelling' and 'severe cell degeneration' and the homogenizing cell change as described by Spielmeyer in 1922 (Fig. 14).

The development of the cellular changes seemed to follow a certain sequence: First the contours of the cell became blurred Then both the cytoplasm and the nucleus swelled and stained diffusely, accompanied by peripheral displacement of the nucleus Subsequently the margins of the cell became ragged or eroded into bays, and vacuoles appeared in the cytoplasm. Parallel to these changes the Nissl substance became pale and the periphery of the nucleus poorly stained.

A

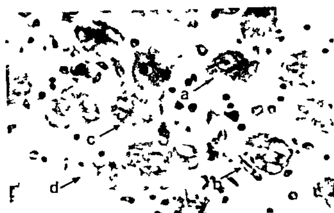
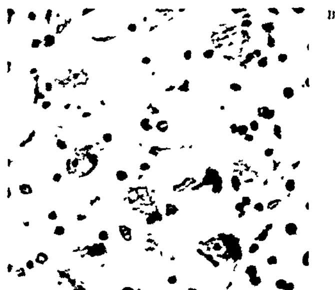


Fig 12 Nucleus cochlearis ventralis Case No 21 Neurons in various stages of disintegration Thionine stain A × 350 B × 500 a nearly normal looking cell with peripherally situated nucleus b cell with vacuolated cytoplasm nucleus still visible c cell with disintegrating nucleus d disintegrating vacuolated cell

A



B

Fig 13 Nucleus cochlearis dorsalis Case No 14 Neurons in various stages of disintegration Thionine stain A × 350 B × 500

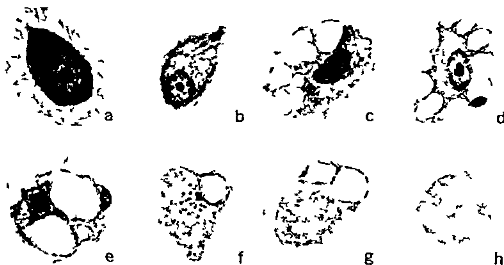
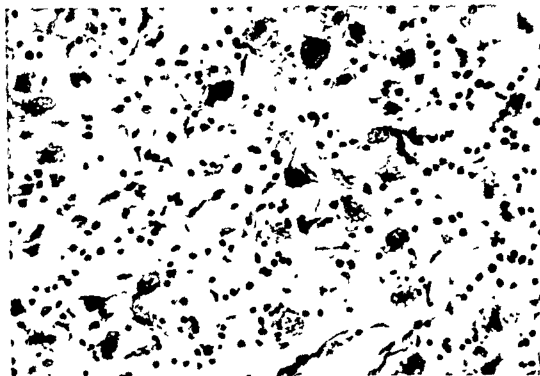


Fig 14 Nerve cells from the cochlear nuclei of asphyxiated babies a normal cell b–h various stages of cell degeneration b peripheral dislocation of nucleus c d vacuolization of cytoplasm e confluent vacuoles f disintegration of nucleus g h ghost cells Thionine stain Drawing × 920



Fig 15 The dorsal cochlear nucleus A moderate loss of nerve cells case No 18 B heavy loss of nerve cells case No 24 Thionine stain × 30



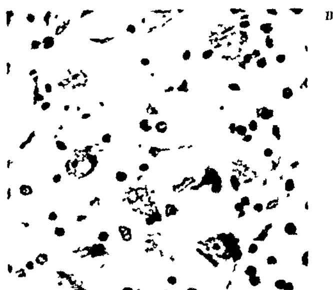


Fig 13 Nucleus cochlearis dorsalis Case No 14 Neurons in various stages of disintegration Thionine stain A × 350 B × 500

station of the auditory system (Rose and Galambos 1952) occupies the lateral part

It was more densely populated with cells than the magnocellular division Its cells were polygonal, round, or oval, with a round or oval nucleus This nucleus often seemed to be placed peripherally, with one of its borders only separated from the surrounding media by a fringe of cytoplasm In several of the premature cases, the cells seemed to be in development, as the cytoplasm only consisted of a barely visible edge surrounding the whole of the more distinct nucleus The staining qualities of the cells appeared good, in the more mature cases, the Nissl substance was visible Only in on case were vacuoles and other signs of degeneration seen in the principal division, while in the magnocellular division these signs were encountered more often

d) The auditive area of the cortex

The evaluation of the findings in the cortex cerebri was not easy, owing to the uncompleted development of the pyramidal cells of the cortex in these cases A number of the preparations showed many small, undifferentiated cells that might possibly be mistaken for macroglia In the pyramidal layers, these were mingled with small cells, bearing only a resemblance to a full grown pyramidal cell, their nucleus only surrounded by a rim of cytoplasm Nevertheless the appearance of the cells and their arrangement showed the usual cortical pattern, but whether the single cells showed any degenerative signs could not be clearly seen In some of the preparations places were found in which a cell loss might be suspected, as the pattern of the cells looked different from the adjacent cortex, the pyramidal cells less apparent, and the space between each cell greater than elsewhere However, small cells with merely a visible border of cytoplasm may represent normal pyramidal cells seen during development, or neuroblasts And secondly, according to Spielmeyer (1922) an evaluation of the normal density of cells must be performed with great care, especially at the crest of a gyrus

This must be remembered when estimating the number of cells in the auditory area of the cortex as this area is situated in the superior part, or at the crest of the anterior transverse temporal gyrus (Ades 1943)

From this description of the microscopic findings it is evident that the cochlear nuclei showed degenerations far exceeding those found in other regions

Therefore the further investigation was concentrated on these nuclei, and cell counts were introduced to establish whether the qualitative findings could be confirmed by quantitative assays

The cell counts

Control cases

The number of cells in the cochlear nuclei of the control cases was counted in two different ways, below called the P and the C method as described above under the heading 'Material and methods'

In some cells the final stage of disintegration was characterized by complete disappearance of the Nissl granules, the nucleus, and the nucleolus, leaving merely a light bluish shadow of a cell body, a 'ghost cell' In other cells the vacuoles were enlarged, and confluent, surrounding the nucleolus and some chromatine remnants

In some cells the borders of the cytoplasm were discernible, in others they had disintegrated, and only fragments of the cell bodies remained

The described changes were most easily recognized in the voluminous cells of the ventral part of the ventral nucleus, but were not so obvious in the smaller cells of the dorsal nucleus

In the heavily affected brains patches containing less cells than normal were conspicuous in the dorsal nucleus (Fig 15), less so in the ventral nucleus

Usually, all the described changes were found side by side, often in a single section, but the heavily affected cells like the ghost cells or those containing confluent vacuoles were in a minority

In the severe cases a certain proliferation of the glia was evident, and in some cases, hyperplasia of the cells in and around the walls of the vessels was observed, leaving the impression of sprouting capillaries

Cells in adjacent parts of the medulla were also affected Changes were found in the olive, the superior olivary complex and the Purkinje cells of the cerebellum, but nowhere did the changes seem to be so striking as in the cochlear nuclei

b) The inferior colliculi

In a few cases the nerve cells of the nuclei of the inferior colliculi also showed signs of degeneration but not nearly to the same degree as those in the cochlear nuclei Only less than one-fourth of the investigated cases seemed to be affected, and none heavily Usually a distinct nucleus of the inferior colliculus was seen, containing the largest cells centrally, and the greatest number of cells ventrally

The cells were polygonal oval, or spindle shaped, richly loaded with chromatine, and with a distinct nucleus and marked boundaries of the cytoplasm

Only one case was seen in which a loss of cells in the dorsal part of the inferior colliculus was suspected, and this was a baby asphyxiated for more than five days In another case asphyxiated for 1 day and 4 hrs, several degenerative signs were found but the severity of these could not be compared to those of the primary nuclei of the same specimen Others presented slightly pathological cells, usually only found in a part of the nucleus, which might well have been artifacts

The cells of other nuclei or pathways seen in these preparations, such as those of the nucleus of nervus V or VII, the cells of the medial lemniscus, or the longitudinal medial fasciculus, were all found to be normal

c) The medial geniculate body

The two divisions of this nucleus the principal and the magnocellular divisions, could be distinguished in the preparations, though no distinct border between the two could be drawn The principal division, considered to be the main relay

station of the auditory system (Rose and Galambos 1952, ...
part

It was more densely populated with cells than the ... cells were polygonal, round, or oval, with a round ... often seemed to be placed peripherally, with one ... from the surrounding media by a fringe of cytoplasm In several ... cases, the cells seemed to be in development, as the ... of a barely visible edge surrounding the whole of the ... staining qualities of the cells appeared good, in the ... substance was visible Only in on case were vacuoles and ... tion seen in the principal division, while in the magnocell... signs were encountered more often

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be confirmed by quantitative assays

The cell counts

Control cases

The number of cells in the cochlear nuclei of th... in two different ways below called the P and the ... under the heading 'Material and methods'

case 26

The first method presumably gives preference to the peripheral zone of the nuclei, whereas in the second method the central parts of the nuclei were favoured The number of cells in the cochlear nuclei of the control cases is seen in Table 4.

TABLE 4

	Both nuclei		Dorsal nucleus	
No	P	C	P	C
15r	87,700	85,900	20 200	20,200
15l	96,000	83,000	20,000	19,100
31	92,900	98,400	*	
34	94,400	90,900	29,000	27,500
39	112,500	111,300	23 500	23,200
45	102,400	95,500	30 200	29,800
51	100,200	92,900	26,200	28,300
57	87,600	91,600	31,200	30,400
59	95,000	93,400	26,800	26,400
60	95,400	95,400	21,700	21,400

r = right, l = left side

* Part of the dorsal nucleus missing

P method Mean cell No 96,400, standard deviation 7,500

C method —»— 93,800, —»— 8,000

Student's t test, double-tail, gives $P \approx 0\ 46$

The observed difference may therefore well be due to chance.

Asphyxiated cases

The number of cells in the cochlear nuclei of the asphyxiated cases was then counted (Table 5)

TABLE 5

No	Both nuclei	Dorsal nucleus
2	39 100	7 000
3	53 200	14 200
4	71 500	9 100
5	57 000	10 900
7	46 200	9 500
10	59 900	9 100
11	56 900	10 800
12	46 500	8 700
14	43,300	7 700
16	42 300	9 400
17	59 800	12 300
18	39 500	13 800
19	43 200	7 900
20	52 600	14 200
21	57 600	12,200
22	84 900	20 500
23	66 200	21 100
24r	43 [illegible]00	5 000
24l	37,300	6 300
26	—	13 000
27	39 300	8 700
28	63 300	14 400
29	65 900	16 200
30	80 700	16 300
32	78 100	20 700
33	42 500	9 600
35	63 [illegible]00	10 900
38r	47 000	6 900
38l	54 900	9 200
40	79 000	16 700
41	63 500	10 300
42	61 200	8 700
43	56 600	8 700
47	57 800	10 100
48	74 900	13 500
49	54 900	12 500
52	60 [illegible]00	8 800
53	59 700	10 700
54	95 300	19 000
55	86 000	19 000
58	73 500	17 400

r = right l = left side

A total of 39 cases. Two of these, cases 24 and 38, are counted bilaterally, and in one case, 26, only the dorsal nucleus is counted

The cases were then divided into four groups, according to their total asphyxiation time calculated from the case records (Table 6 and Fig 16)

TABLE 6 *Number of cells related to approximate time of asphyxiation*

	No	Time Days	Time Hours	Both nuclei	Dorsal nucleus
0–10 hrs	54		4	95 300	19 000
	30		5	80 700	16 300
	32		5 6	78 100	20 700
	48		6 7	74 900	13 500
	22		7–8	84 900	20 500
	4		9	71 500	9 100
	3		9 10	53 200	14 200
	58		8 12	73 500	17 400
10 hrs 1 day	40		9 12	79 000	16 700
	17		10–11	59 800	12 300
	33		11	42 500	9 600
	21		11	57 600	12 200
	5		12	57 000	10 900
	47		12	57 800	10 100
	12		13	46 500	8 700
	19		13	43 200	7 900
	55		11 20	86 000	19 000
	29		15	65 900	16 200
	41		15 20	63 500	10 300
	2		20	39 100	7 000
	10		22	59 900	9 100
1 2 days	24r		24	43 700	5 000
	24l		24	37 300	6 300
	28	1	2 6	63 300	14 400
	14	1	4	43 300	7 700
	11	1	5	56 900	10 800
	18	1	6	39 500	13 800
	26	1	8	—	13 000
	20	1	8	52 600	14 200
	23	*1*	*7 10*	*66 200*	*21 100*
	53	1	10	59 700	10 700
	49	1	10	54 900	12 500
	35	1	11 12	63 700	10 900
	27	1	18 19	39 300	8 700
> 2 days	42	2	15	61 200	8 700
	43	3	10	56 600	8 700
	52	3	13	60 700	8 800
	7	5	20	46 200	9 500
	38r	7	7	47 000	6 900
	38l	7	7	54 900	9 200
	16	14		42 300	9 400

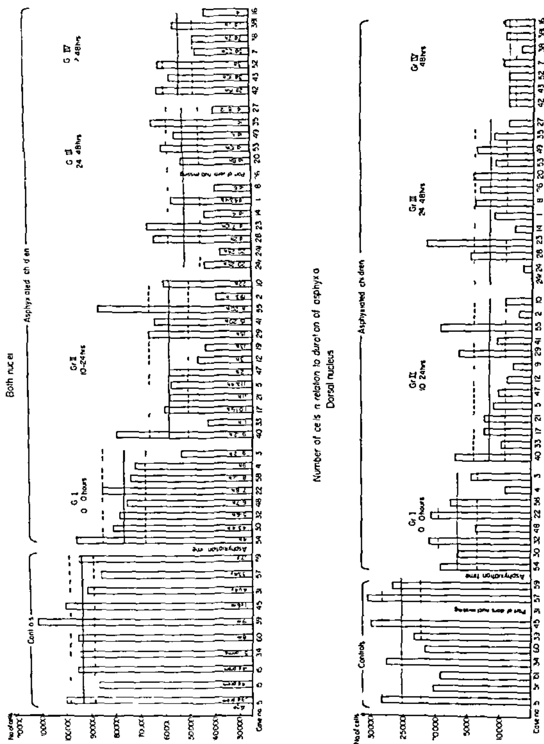


Fig 16

The drawn lines represent the group means, M, and the stippled lines group means ± 2 standard errors of the mean, $M \pm 2\,\epsilon(M)$ (p 69)

As it might be objected that an exact asphyxiation time would be difficult to obtain from the case records the cases were also divided into 3 groups according to their exactly known survival time (Table 7 and Fig 17)

TABLE 7 *Number of cells related to the lifetime of the asphyxiated babies*

Lifetime	No	Days	Hours	Minutes	Both nuclei	Dorsal nucleus
	54		4	18	95 300	19 000
	30		4	45	80 700	16 300
	32		7	20	78 100	20 700
	4		9	5	71 500	9 100
	3		9	30	53 200	14 200
0–1 day	17		10	30	59 800	12 300
	33		11	10	42 500	9 600
	5		11	55	57,000	10 900
	22		12	6	84 900	20 500
	19		13		43 200	7 900
	29		15	10	65 900	16 200
	2		19	57	39 100	7 000
	11	1	4	48	56 900	10 800
	26	1	8		—	13 000
	20	1	8	5	52 600	14 200
	10	1	8	5	59 900	9 100
	28	1	9	5	63 300	14 400
	48	1	9	55	74 900	13 500
1 2 days	12	1	11	15	46 500	8 700
	35	1	11	25	63 700	10 900
	23	1	14	5	66 200	21 100
	53	1	14	15	59 700	10 700
	55	1	18	30	86 000	19 000
	27	1	18	30	39 300	8 700
	40	2	1	30	79 000	16 700
	18	2	4	20	39 500	13 800
	21	2	14	50	57 600	12 200
	58	3		50	73 500	17 400
	47	3	1	8	57 800	10 100
	14	3	1	50	43 300	7 700
	41	3	15	15	63 500	10 300
> 2 days	24r	4	1	15	43 700	5 000
	24l	4	1	15	37 300	6 300
	42	5		45	61 200	8 700
	43	5	7	15	56 600	8 700
	52	5	12	45	60 700	8 800
	7	5	20		46 200	9 500
	49	10	19	5	54 900	12 500
	16	16			42 300	9 400
	38r	22			47 000	6 900
	38l	22			54 900	9 200

r right l left side

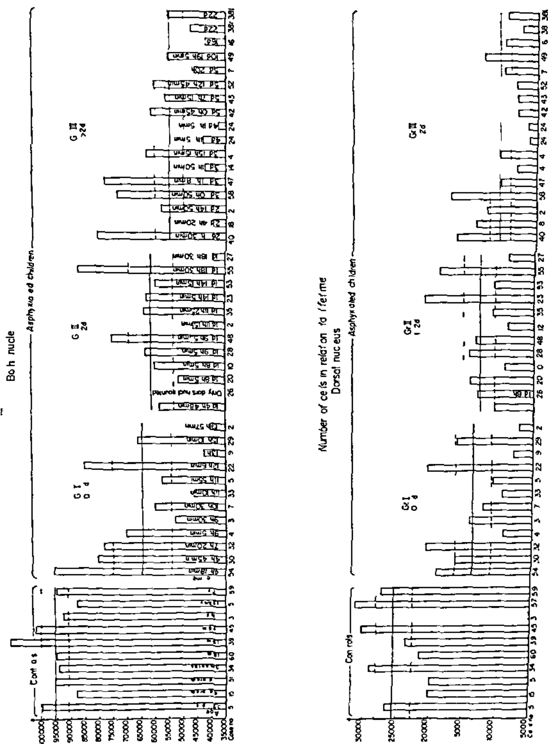


Fig 17

The drawn lines represent the group means M and the stippled lines group means ± 2 standard errors of the mean M ± 2 e(M) (p 69)

The first group in Table 7 covers the survival period 0–1 day, and not 0–10 hours, as there were only 5 cases that lived less than 10 hours The comparison between the groups would have less significance if, for instance, group No 1 should contain 5, and group No 4, 17 cases

Twins

An interesting observation in these cases are the cell numbers in the cochlear nuclei of twins There are 6 twin births, representing about 10% of the total series The frequency of multiple births among prematures in the obstetric departments in Oslo is 18 8% (Daae Blegen 1953) However, among these twins only 4 pairs were obtained Their data are shown in Table 8

TABLE 8

Pair No	Case No	Volume, mm³	Total No of cells	Asphyxiation time
1	3	2 8	53,200	9½ hrs
	4	3 2	71,500	9 "
2	40	3 6	79,000	9–12 hrs
	41	3 0	63,500	15–20 "
3	42	3 1	61,200	2d 15 hrs
	43	3 0	56,600	3d 10 "
4	54	4 1	95,300	4 hrs
	55	4 3	86,000	11–20 "

Pairs Nos 2 and 3 in all probability were homozygotic, the others were born in private clinics, and data about the placenta were not recorded The twins were of the same sex in all pairs, and their brain weights were practically identical

It is seen that the volumes of the cochlear nuclei are of practically the same size As a possible intrauterine asphyxia in these cases would have had about the same influence on both babies, it is interesting to note that in every case the twin having suffered from neonatal asphyxia for the longer period shows the lower number of cells in the cochlear nuclei

Summary of observations in the human series

The cochlea

Seventy-two temporal bones were obtained from the 39 asphyxiated children In three of the cases perfusion was not performed, and in the six corresponding preparations of the inner ears the postmortal changes were so extensive that no evaluation was possible The same was true in 11 of the first formaline perfused cases, from which 19 temporal bones were prepared

The remaining 47 preparations from the asphyxiated cases are described

In the control material, 10 temporal bones were obtained, but only in the single case which was perfused was an evaluation of the findings possible on both sides

This makes a total of 49 specimens in which a description of the cochlea is given

In the control case, a normal preparation was found on the right side, but on the left the supporting elements were distorted and the cytoplasm of the ganglion cells shrunken In the asphyxiated cases, 13 preparations corresponded to the description of a normal cochlea In 7 of these the only finding was some blood in the perilymphatic spaces

In 11 other preparations, only one of the following minor changes was found a bend in the basilar membrane, detachment of the vestibular ligament with wavy vestibular membrane, some shrinking of the cytoplasm in some of the ganglion cells or a slight vacuolization in the region of the inner hair cells As these changes, in the author's opinion, represent preparational artifacts, it can be concluded that in 24 of the 49 specimens the inner ears were found to be normal or nearly normal

In the remaining 25, one or several of the following changes were noted

Compression of the organ of Corti in 11 cases

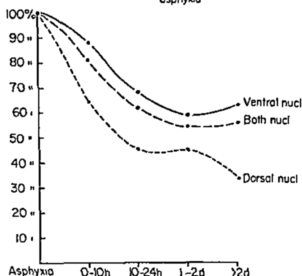
Vacuoles and space formation in the region of the inner hair cells in 6 cases

A shrunken cytoplasm and pycnotic nuclei in the cells of the spiral ganglion in 6 cases

Bends or tears in the basilar membrane, detachment of the spiral ligament in 4 cases and blood in the perilymphatic spaces in 4 cases

In the author's opinion these irregularities indicate either autolytic changes, or mechanical distortions occurring during the preparation This will be discussed more thoroughly later

The important point, however, is the condition of the hair cells, which were normal in all but three preparations In these three a shrunken cytoplasm and indistinct borders of the hair cells were found bilaterally in the first case, only in the upper coils in the second, and only on the left side of the third case


Loss of nerve cells in the cochlear nuclei in cases of asphyxia neonatorum, in relation to duration of asphyxia
100%
90 "
80 "
70 "
60 "
50 "
40 "
30 "
20 "
10 "
Ventral nucl
Both nucl
Dorsal nucl
Asphyxia
0-10h
10-24h
1-2d
>2d

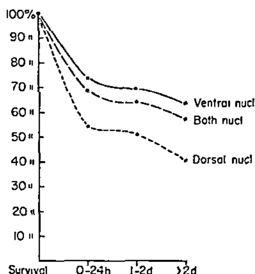

Loss of nerve cells in the cochlear nuclei in cases of asphyxia neonatorum, in relation to survival time
100%
90 "
80 "
70 "
60 "
50 "
40 "
30 "
20 "
10 "
Ventral nucl
Both nucl
Dorsal nucl
Survival
0-24h
1-2d
>2d

Fig 18

The cochlear nuclei

In the control cases the volume of the cochlear nuclei varied between 5 2 mm³ in those less than a year of age, and 10 5 mm³ in those more than ten years old

In the younger asphyxiated children, those more than 3 months premature, the volume was 2 6 mm³, in the full term, 3 6 mm³

The cochlear nuclei in the control material contained an average of 96,400 cells, and the dorsal nucleus alone averaged 25,400 cells

The asphyxiated cases were divided into four groups, asphyxiated 1–10 hours, 10 hours 1 day, 1–2 days, and more than 2 days respectively

In group 1 the average cell number was 76,500, in group 2, 58,300, group 3, 51,700 and in group 4, 52,700 cells In the dorsal nucleus the corresponding numbers were Group 1, 16,300, group 2, 11,500, group 3, 11,500, and group 4, 8,700 cells

If this loss of nerve cells is calculated in per cent of the normal cell numbers (Fig 18 and Table 14), it is found that in the whole nuclear complex, dorsal and ventral nucleus, 20 % of the cells were lost after 10 hours of asphyxia, 40 % after the first day, and more than 45 % of the cells were lost after two days of asphyxia or more

In the dorsal nucleus 36% of the cells were lost after 10 hours, 55%, after the first day, and 66 % after more than two days

Because the reported asphyxiation time may be somewhat unreliable, the number of cells was also calculated in relation to the exactly known lifetime of the babies

As a corresponding and increasing loss of nerve cells was also found with increasing lifetime, it can be postulated that the longer a baby lives in an asphyxiated state, the fewer are the cells found in the cochlear nuclei

The experimental material

The cochlea in kittens

The age of the 29 kittens varied from 22 hours to 19 days The human cochlea at this age is fully developed but in kittens it is still in the last stages of development This was evident in both the controls and the asphyxiated kittens, as the tunnel of Corti in the younger specimens was only open in the basal coil, which is first developed In the apical coils some mesenchymal tissue still filled the tunnel Only in some of those 2 3 weeks old was the tunnel open in all coils The fluid spaces inside the organ of Corti were only incompletely developed, and mesenchymal tissue was found inside the middle ear in the younger kittens Apart from these differences the appearance of the cochlea of kittens corresponds essentially to that of the human cases (Fig 19)

Control kittens 1–6 As only smaller variations were found between these six preparations they are described together

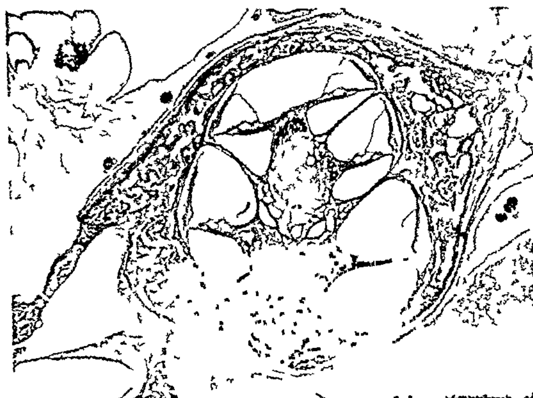


Fig 19 The cochlea of asphyxiated kitten case No 22 × 22

The fixation and preparation are moderately good but still certain regions show preparational defects which will be described However all the main features of the organ of Corti and the spiral ganglion can be observed

In the apical and middle coils the tunnel is not fully open in cases Nos 1 5 and 6 which were only 4 days old The outer hair cells are well prepared but the inner hair cells are short shrunken with a poorly stained cytoplasm In the border cells and the inner phalangeal cells the cytoplasm is often vacuolized The stria vascularis has a normal appearance but some blood is seen in the vessels The papilla basilaris is low The cells of the spiral ganglion are normal

Asphyxiated kittens

1 This preparation has been successful all the details of the organ of Corti may be recognized The outer and inner hair cells are developed and contain stainable nuclei and the tectorial membrane lies in its normal place. The vessels of the organ of Corti are filled with blood The spiral ganglion seems normally developed and no pathological findings can be reported

2 This is also a normal preparation of the inner ear in the kitten

3 Like Nos 1 and 2

4 In this preparation only the nuclei remain in the inner hair cells and the border cells Their cytoplasm is vacuolized or partly disintegrated There is some compression of the papilla basilaris and the vestibular membrane is adherent to the limbus The rest of the organ of Corti and the spiral ganglion look normal

5 In the region of the inner hair cells changes are seen similar to those described in No 4, otherwise a normal preparation

6 Technically, not a very successful preparation The inner and outer hair cells are fairly well preserved but the whole organ of Corti is compressed, and the tectorial membrane is thinner than normal The stria vascularis, however, has a normal appearance, and the cells of the spiral ganglion are of normal size, and contain round, apparently normal nuclei Inside the ganglion well defined nerve bundles are observed

7 The cytoplasm of the inner hair cells is shrunken and poorly stained The outer hair cells look normal The organ of Corti is also compressed in this preparation, especially in the apical and middle coils, the basal coil is the best preserved The cells of the spiral ganglion look normal

8 A fairly successful preparation However, the organ of Corti is somewhat compressed, and there is a shrinkage of the cytoplasm in the area of the inner hair cells

All the other features of the cochlea correspond to the normal description

9 The organ of Corti was destroyed during removal of the bone

10 Some compression of the organ of Corti, and also in this preparation there is some shrinkage of the cytoplasm in the area of the inner hair cells Otherwise the preparation shows normal features

11 Not a very successful preparation as the organ of Corti is compressed the limbus is low and the cytoplasm of the inner hair cells, the inner phalangeal cells and the border cells is disintegrating The hair cells are present, but their cytoplasm is homogeneous

12 In this preparation the supporting cells except the pillar cells are all empty only the framework persists Of the Hensen cells only the nuclei remain in the proximal part In the external sulcus the cells are swollen and vacuolized, in the spiral ganglion the cells show shrinkage and homogenization of the cytoplasm The hair cells however look normal and the tectorial membrane has a normal form

13 The vessels are filled with blood There is some compression of the organ of Corti the cuboidal surface layer of the stria vascularis is flattened, as are

obular formation is seen at its surface Vacuolization is seen in the region cf ie inner hair cells However, the different details of the organ of Corti are re- ognizable, the nuclei of the hair cells are round, the cells of the spiral ganglion e well preserved

14 A normal preparation, corresponding to the control cases

15 In this preparation, derived from a kitten which was found dead in its ige on the night before perfusion, the organ of Corti and the surroundings how extensive changes

The stria vascularis is thick, swollen, and oedematous The cuboidal cells on s inner surface are partly detached, the organ of Corti has lost its configuration, nd cell remnants are scattered around in the ductus cochlearis The tectorial nembrane is partly torn to pieces, partly drawn out to resemble a thin veil, and as no relation to the organ of Corti.

The basilar membrane is oedematous In the spiral ganglion cells the nuclei re pycnotic and the cytoplasm vacuolized, homogeneous, and partly disinte- grating

As this kitten had been dead about 12 hours before perfusion was performed, he reported changes obviously represent a heavy postmortal autolysis The degenerations presented are more pronounced than in any of those previously described and the preparation is thus of great interest for comparison

16 In this preparation from a four-day-old kitten, the tunnel of Corti is not yet fully developed, but the fluid spaces around the outer and inner hair cells are present

The appearance of the organ of Corti, the stria vascularis, and the spiral ganglion is normal

17 This preparation shows normal features of the outer and inner hair cells, the stria vascularis, and the ganglion cells The organ of Corti and its develop- mental stage may be studied in detail (Fig 20) and it is possible, especially from this preparation, to evaluate how the tunnel and the fluid spaces within the organ of Corti start to develop in the basal coil In this specimen the tunnel formation has proceeded approximately to the middle of the cochlea More apically, the outer and inner pillar cells lie in contact The tonofibrils of the pillar cells are developed in the basal coil, where their cytoplasm is thinner than in the upper coils

18 The hair cells are well preserved, the tunnel of Corti is not fully developed, it is seen only in the basal coil Inner and outer hair cells are normal It is possible in this preparation to evaluate how the fluid spaces are formed by a retraction and a diminution of the cytoplasm of the cells bordering the tunnels

The bony walls of the cochlea are a little less developed than in the control preparations but this animal died when it was only 22 hours old

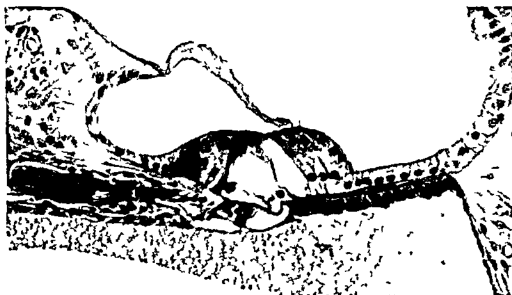


Fig 20 Asphyxiated kitten Case No 17 Basal coil × 340

19 In this case the preparation is fairly good but in the helicotrema the epithelium is detached from the bony wall In the basal coil the fluid spaces inside the organ of Corti are fully developed, but higher up these spaces are not yet formed There is a bend in the basilar membrane in the basal coil, and detachment of the tectorial membrane at the same place Otherwise the findings are normal

20 In this preparation there is no detachment of the epithelia from the bony walls and the basilar membrane is straight Otherwise the preparation is similar to No 19

21 A normal preparation no pathological changes are found

22 In this case the tunnels inside the organ of Corti are developed in every coil The mesenchyme in the middle ear is reduced The stria vascularis is exceptionally well preserved and its cuboidal epithelium is regular No pathological changes are found except some breaks in the vestibular membrane (Fig 19)

23 The perfusion in this case has not been very successful The region of the inner hair cells is not well preserved vacuoles and disintegration are seen in the cytoplasm of the inner hair cells and the border cells The tectorial membrane is detached and the cytoplasm of the ganglion cells is homogenized and shows some shrinkage The outer hair cells the basilar membrane and the stria vascularis appear normal

The cochlear nuclei in kittens

The cochlear nuclei in the kitten largely show the same topography as in man (Figs. 21, 22), but certain differences are evident, both in the macroscopic and microscopic appearance. The average volume of the cochlear nuclei in kittens is seen in Table 9. The average length of the dorsal nucleus in the new-born kittens was 1.2 mm, of the ventral nucleus 2.1 mm, and the length of the whole nuclear complex was 2.4 mm.

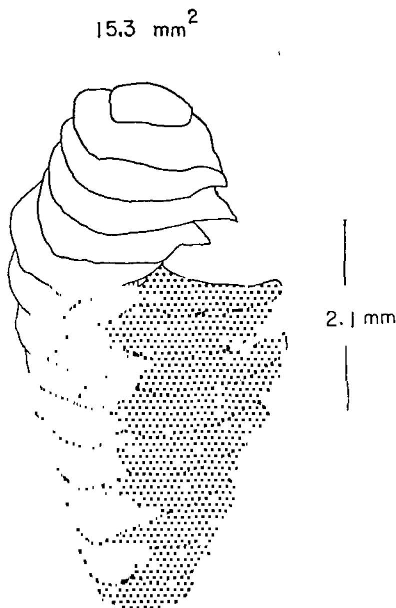


Fig 21 Drawings of serial sections of the cochlear nuclei in a new-born kitten Every 10th section is drawn. Dorsal nucleus dotted, posteroventral nucleus hatched.



Fig 22 The cochlear nuclei in kitten A caudal level B middle level, C oral level d dorsal av, anteroventral, pv, posteroventral nucleus The arrow in B points to the pyramidal cell layer Control kitten No 12 *Thionine stain × 30*

The dorsal cochlear nucleus seen in transverse sections is more elongated than in man, with a broad and club-like ventral part The part lying laterally to the restiform body, which in man is the broadest, is narrow in the kitten (Fig 22C) Microscopically both the ventral and the dorsal nuclei contain the same layers as described in the human counterpart, but in the dorsal nucleus the third, pyramid or spindle cell layer, constitutes a characteristic band, two to three cells thick, with their long axis perpendicular to the surface This layer continues throughout the length of the dorsal nucleus Fibres of the acoustic

TABLE 9 *Average volume of the cochlear nuclei in kittens (in mm³)*

	No of cases	Both nuclei (mean value)	Standard deviation
Control kittens			
Newborn 1 day	6	1 9	0 3
1 day–1 week	7	2 2	0 9
1 2 weeks	6	3 0	0 8
> 2 weeks	7	3 9	0 7
Asphyxiated kittens			
Premature	7	0 6	0 1
1 day–1 week	6	1 3	0 3
1–2 weeks	7	2 0	0 3
> 2 weeks	8	2 2	0 3

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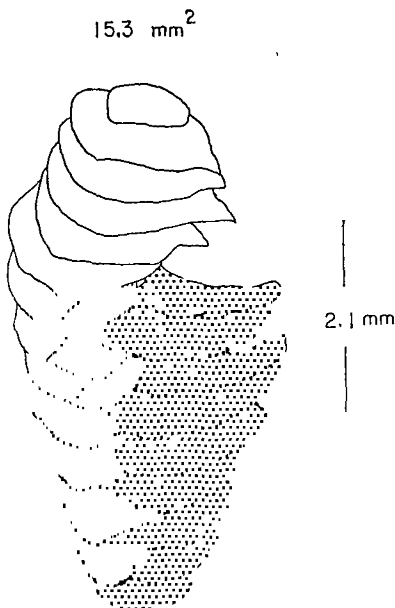


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1 day 1 week	7	2 2	0 9
1 2 weeks	6	3 0	0 8
> 2 weeks	7	3 9	0 7
Asphyxiated kittens			
Premature	7	0 6	0 1
1 day–1 week	6	1.3	0 3
1–2 weeks	7	2 0	0 3
> 2 weeks	8	2 2	0 3

striae separate the dorsal from the ventral nucleus Between these and the pyramidal cells is the middle layer, containing the main part of the nerve cells

The ventral nucleus can be divided into an antero ventral and a postero ventral portion (Fig 22B) The cells are spherical, with a round or oval nucleus a distinct nucleolus and abundant cytoplasm with a fine and evenly distributed Nissl substance The cells are smaller in new-born kittens than in new born human babies Seen in transverse sections this nucleus is also pear-shaped in the kitten, the stalk end pointing dorsomedially, the nerve entering ventromedially

The microscopic examination of the cochlear nuclei in the asphyxiated kittens did not reveal any cell changes comparable with those found in the human preparations

The cell counts in kittens

Cell countings were then performed

The results of the investigations in kittens are summarized in Tables 10–14 and in Figures 23 and 24

TABLE 10 *Number of cells in the cochlear nuclei in normal kittens**

Litter No	Kitten No	Age	No of cells
	1	2 days	93 400
1	3	14 ″	119 000
	4	14 ″	99 500
	5	30 ″	104 500
2	8	Newborn	99 200
	9	7 days	107 400
	12	Newborn	125 100
3	13	7 days	126 000
	14	14 ″	103 500
	15	21 ″	104 800
	16	1 days	90 400
	17	1 ″	110 600
4	18	9 ″	105 700
	19	16 ″	107 100
	20	23 ″	104 600
	21	Newborn	111 300
	22	″	104 600
5	24	7 days	108 800
	25	14 ″	100 900
	26	18 ″	110 500

* Nos 2 6 7 10 11 and 23 were deceased

Control kittens

In Table 10 the number of cells in the cochlear nuclei of 'normal' or non-asphyxiated kittens is shown, grouped according to their litters and in Table 11 the same animals are grouped according to their lifetime.

As appears from Table 10, an attempt has been made to obtain within each litter a representation of the ages new-born, 1, 2, and 3 or 4 weeks, in order to see whether there are, in kittens, any indications of postnatal increase in the number of nerve cells.

In Table 11 the normal kittens are arranged according to age and in this Table the 6 control kittens are also included, one from each litter of the asphyxiated animals.

As appears from the figures, the number of cells is of the same order at all stages from new-born to 4 weeks.

TABLE 11 *Number of cells in the cochlear nuclei of normal kittens grouped according to their age*

Newborn	0–1 week	1–2 weeks	2–4 weeks
99 200	90 400	105 700	120 600*
125 100	110 600	121 400*	107 100
111 300	93 400	119 000	110 500
104 600	103 800*	99 500	117 500*
	126 000	103 500	104 800
	99 200*	100 900	104 600
	95 300*		104 500
	108 800		
	107 400		

* – Control kittens from the asphyxiated litters

Asphyxiated kittens

Table 12 and Fig 23 show the number of cells in the cochlear nuclei of asphyxiated kittens grouped on the basis of duration of asphyxiation. The number of cells found in premature kittens is also shown. As these suffered from asphyxia during their whole life span the asphyxiation time and the lifetime are the same.

It is seen that the number of cells in the cochlear nuclei of premature asphyxiated kittens corresponds to that in kittens postnatally asphyxiated from ¾ to 18¾ hours.

Table 13 shows the number of cells in the cochlear nuclei of asphyxiated kittens grouped according to their age for comparison with the normal kittens.

TABLE 13 *Number of cells in the cochlear nuclei of asphyxiated kittens grouped according to age*

One week premature	0–1 week	1–2 weeks	2–3 weeks
92 300	104 900	113 000	106 500
113 700	96,600	95,600	95 600
92,500	94 500	99 100	115,900
89 400	99 800	91 300	108 000
92 300	103 700	105 200	98,100
95 000	90 000	111 200	105,100
94 200	92 000	108 700	101 500
			111 300

It is seen that these numbers correspond to those of the normal kittens, shown in Table 11

In Figure 24 the different age groups of normal and asphyxiated kittens are placed next to each other, showing in one Figure all the findings in the experimental material

The stippled lines show the standard deviation within each group It is seen that in each of the four groups the range of the values in the asphyxiated cases lies within those of the controls

The lowest number of cells 95,600 was found in the one week premature kittens and the highest number of cells 110,000, was found in the new-born controls A significance test (Student's t-test double-tail) applied to the difference between these group means gave the result

t – 2 5 P 4 4%, which is significant at the 5% level but not at the 1% level However, this is a comparison between extreme values, and in addition the cells in the cochlear nuclei of ens were so small some may have been missed

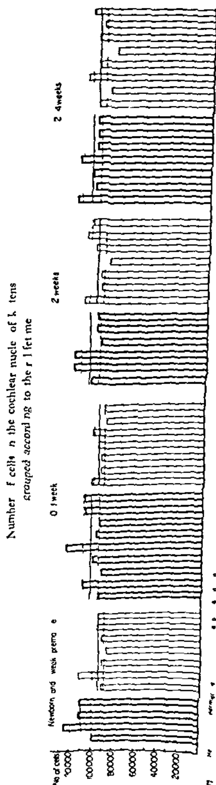
A comparison between the other correspo did not show cant difference between the number of cells ated kittens an controls

A regression analysis perf e co up the pre kittens shows that there is n the nu th age

Summary of

The cochlea in kittens

In the 23 asphyxiated kitten litters the temporal bones were laterally, in the rest on one side or



Number of cells in the cochlear nuclei of kittens grouped according to their lifetime

The drawn lines represent the group means M and the stippled lines group means ± 2 standard errors of the mean M ± 2 (M) (p 19)

Fig 24

The methodological errors

The total methodological error is given by the following formula

$$V_t = \sqrt{(S_d)^2 + (S_p)^2 + (S_c)^2}$$

where S_d represents the drawing error, S_p the planimeter error, and S_c the counting error, all expressed as percentages of means, i.e. coefficient of variation.

The counting error

The counting error has been estimated in the following way: in 18 cases of both nuclei and in 17 cases of the dorsal nucleus countings were performed twice in the same way according to the P method. In all 1936 units were counted in 262 slides for both nuclei and 542 units in 116 slides for the dorsal nucleus.

The average error of counting is then given by the formula

$$S_c = \sqrt{\frac{\Sigma d}{2N}} \times 100 / \text{Mean count},$$

in which d is the difference between the two determinations and N is the number of sets of nuclei.

The results are

Both nuclei $S_c = 3\ 3\%$

Dorsal nucleus $S_c = 4\ 9\%$

The planimeter error

The planimeter error has been estimated in the following way: planimetry was performed three times in every 10th section of 12 cases for both nuclei and in every 10th section of 11 cases for the dorsal nucleus. In all the planimeter error was calculated from 507 measurements of both nuclei and 234 measurements of the dorsal nucleus.

The planimeter error is then given by the formula

$$S_p = \sqrt{\frac{\Sigma S}{N}} \times 100 / \text{Mean area}$$

where ΣS is the sum of variances for all nuclei and N is the number of nuclei. Mean area [illegible] the added average superficial content of every 10th section in 12 or 11 nuclei.

The results are

Both nuclei S_p [illegible] 0 9

Dorsal nucleus S_p [illegible] 0 [illegible]%

The drawing error

The drawing error cannot be estimated directly, as the figures arrived at after planimetry include both the drawing and the planimeter errors. However, the drawing error may be calculated indirectly, from these combined errors and the already found planimeter error.

In 10 nuclei the circumference of both nuclei was drawn twice, applying the Bausch and Lomb projection apparatus. Then on each drawing planimetry was performed three times and the average of these was found. In all both nuclei were drawn 276 times and the dorsal nucleus 144 times.

Planimetry was performed 828 times for both nuclei and 432 times for the dorsal nucleus.

The average error, including both the drawing and the planimeter errors is then given by the formula

$$S_b = \sqrt{(S_d)^2 + (S_p)^2} = \sqrt{\frac{\Sigma d^2}{2N}} \times 100 \,/\, \text{Mean area}$$

where d is the difference between the two determinations and N is the number of nuclei.

The results are

Both nuclei $S_b = 2.3\%$

Dorsal nucleus $S_b = 5.8\%$

Using the same formula $S_b = \sqrt{(S_d)^2 + (S_p)^2}$ and knowing $S_p = 0.9\%$ and $S_b = 2.3\%$ or 5.8% the drawing error is found

Both nuclei $S_d = 2.2\%$

Dorsal nucleus $S_d = 5.7\%$

Summary of statistics

TABLE 16

	Counting error (S_c)	Planimeter error (S_p)	Drawing error (S_d)
Both nuclei	3.3	0.9%	2.2%
Dorsal nucleus	4.9%	0.9%	5.7%

As an indication of the total error of the method the coefficient of variation (standard deviation in per cent of mean) is employed This coefficient is given by the formula

$$V_t = \sqrt{(S_b) + (S_c)}$$

$$\text{Both nuclei} \quad V_t = \sqrt{2\ 3 + 3\ 3^2} = 4\ 0\%$$

$$\text{Dorsal nucleus} \quad V_t = \sqrt{5\ 8 + 4\ 9} = 7\ 6\%$$

Significance tests performed on the differences between group means

Differences between group means have been tested both by Student s t test (Pearson and Hartley 1962) and by the test proposed by Welch (1947) for comparisons involving two variances which must be separately estimated Both tests led to the same conclusions Significance levels for two sided tests have been assessed by referring the computed t and v values to Tables 12 and 11 respectively of the *Biometrika Tables for Statisticians* (Pearson and Hartley 1962) The tests are summarized in this report in the form of P values showing the probability of getting by pure chance a difference as large as the observed difference, or even larger, in either direction

a) According to asphyxiation time

TABLE 17

	Means		Difference	Student s t test* P ≤
Both nuclei	Controls 96 400	Group 1 76 500	19 900	0 001
	Group 1 76 500	Group 2 58 300	18 200	0 006
Dorsal nucleus	Controls 25 400	Group 1 1[illegible]3[illegible]	9 100	0 001
	Group 1 16 300	G[illegible]ou[illegible] 11[illegible]	4 800	0 014

b) According to survival time

TABLE 18

	Means		Difference	Student's t-test** P ≦
Both nuclei	Controls 96,400	Group 1 64,300	32,100	0 001
	Group 1 64,300	Group 2 60,800	3,500	0 622
Dorsal nucleus	Controls 25,400	Group 1 13,600	11,800	0 001
	Group 1 13,600	Group 2 12,800	800	0 693

* Welch's test led to the same conclusions.

** It is evident from the diagram shown in Table 14 that there will be no significant loss of cells in groups 3 and 4, seen in relation to group 2

Levels of significance

P ≦ 0 10): 10% probability that the difference may be due to chance.

P ≦ 0 05): 5% —»— —»—

P ≦ 0 01): 1% —»— —»—

P ≦ 0 001): 0 1% —»— —»—

DISCUSSION

The human material

The cochlea

The study of the human cochlea has revealed considerable deviations from the generally accepted picture of a normal inner ear These findings naturally raise the question of the extent to which these changes represent artifacts or true pathological changes The difficulties involved in preparing satisfactory specimens of the human inner ear are generally recognized (Kristensen 1949)

As emphasized by Engstrom (1962), very few investigators have succeeded in

overcoming these obstacles in human material, where autolytic changes and mechanical distortions frequently make the evaluation so difficult as to render a definite statement inadvisable

In order to obtain good results it is imperative to perform fixation by perfusion immediately after death However, even so, the fixation fluid for various reasons (e g intravascular coagulation) may by pass the arterial branches to the cochlea, thus facilitating autolysis The autolytic changes are characterized by swelling and homogenization of the cytoplasm, pycnosis of the nuclei, or precipitates and globular formation, as recently described by Fernandez (1958) in the cochlea of man

However, as the technical procedures improved with growing experience, these changes gradually became less pronounced, thus favouring the view that we are dealing here with changes of an artificial nature

Distortions, such as bends of the basilar membrane, tearing of the vestibular membrane or deformities of the pillar cells, constitute another group of changes However, when special precautions were taken in order to secure as far as possible a gentle isolation of the inner ear, changes of this kind were markedly reduced The remaining changes, which are presumably caused by air bubbles or irregular shrinkage of the embedding medium, most likely should be regarded as unavoidable hazards

A feature frequently observed in the present preparations was the much discussed phenomenon of compression of the organ of Corti Compression is characterized by a collapse of the structures of the organ of Corti, sometimes to such an extent that cells frequently cannot be identified (Fernandez op cit) In the present material it was found regularly in the formaline perfused cases but in only two of the Heidenhain Susa preparations, and in both of these the compression was pronounced on only one side This fact strongly supports the statement of Fernandez that compression is an artifact which should not be confused with pathological changes

It is thus seen that the majority of the irregular findings in this material may be explained as being due to artifacts, caused either by autolysis or by mechanical distortions However some findings still remain unexplained, especially those in the stria vascularis and in the region of the inner hair cells

In the evaluation of these findings, the excellent and detailed description of cochlear changes observed after asphyxia by Kimura and Perlman (1956) may serve as a starting point After obstruction of the inferior cochlear vein in guinea-pigs they found initial changes in the stria vascularis, where dilatation of the capillaries and oedema of the epithelium were already noted after one hour After one day the hair cells started disintegrating This was first noted in the basal turn and then in the cytoplasm of the outer hair cells, which became diffuse, and their nuclei dissolved

These findings were more pronounced than those in the present material In the first place Kimura and Perlman reported pallor and atrophy, followed by disintegration of the epithelial layer of the stria vascularis in the early hours after obstruction No such extensive degenerations were noted in the present

cases, only minor ones Secondly, they reported changes ... hair cell which were lacking in the present material In fact the ... well preserved, even in cases where the supporting element ...

The explanation of the minor changes in the stria vascularis ... and especially of those noted in the region of the inner hair cel ... Possibly the preparatory difficulties are responsible ... his great experience in inner ear preparations, emphasizes the ... involved in preservation of these structures With these reserv... the less successful preparations, several cases still remain in whi... appeared quite normal, and the sensory cells especially were we... In these cases it is not likely that the asphyxia had produced an... disorders However, as present techniques do not permit the functional ... of minor structural disturbances, the question of the significance of ... defects as a cause of hearing loss in cases of neonatal asphyxia must be l ... It is likely that in the future more refined techniques, e g histochemical method may extend the possibilities for functional analysis of even minor structural changes

The methods employed in this investigation, however, have revealed no obvious systematic alterations attributable to asphyxia

The cochlear nuclei

The most conspicuous finding in the present investigation is a loss of nerve cells in the cochlear nuclei

In the most severe cases the number of cells was reduced to approximately one-half of the normal average

This result was obtained by counting the nerve cells and computation of the nuclear volume The question naturally arises whether this loss of cells may be explained by methodological errors As emphasized by Agduhr (1941) who discussed the question extensively, hardly any method is available for the determination of the number of cells in a given nucleus which is not encumbered with disadvantages

Methodological errors

The most obvious sources of error in the present investigation are those entailed in counting, drawing and planimetry To reduce these errors to a minimum the following precautions were taken the error of counting the same cell twice was avoided by counting only those nerve cells in which the nucleoli were seen Since it is impracticable to count all the cells, and since the nerve cells are irregularly distributed, another possible source of error is involved in the selection of sample areas, here called units, to be counted Chow (1951) states that care must be taken to distribute the areas sampled throughout the entire nuclear mass

Still the units might be placed involuntarily in spots with high or low density of cells.

In the premature children, where the cochlear nuclei are still small, this error was negligible, as the total of units counted covered the major part of the cross-sectional areas.

In the controls, however, the square area of each nucleus was so great that even the counting of several hundred units covered less than 50% of the area. For this reason the P and the C methods were introduced, but as the statistical evaluation showed (see Table 4) that the observed difference might be due to chance, the results obtained with the P method was used for comparison of the cases.

The method of counting used in this investigation has, as seen in the statistical Tables, an error of 3.3% for both nuclei and 4.9% for the dorsal nucleus alone. The reason for this difference between the two nuclei is probably the smaller size of the cells in the dorsal nucleus, and the consequent possibility of confusion with glial elements.

Other methods of counting were taken into consideration. If photography were employed, the whole nucleus could then be seen in one picture. However, owing to the thickness of the section, a certain number of the cells would be out of focus, especially so when the counting is based on the nucleoli. Various projectors depicting the histological material on an opaque disc were tried, but did not prove satisfactory.

An ideal method, statistically, would be to subdivide the entire nuclear area into squares and count the cells of squares or units picked at random. However, technical difficulties involved in this procedure prevented its practical application. Evaluating advantages and disadvantages, the method employed was deemed to be best fitted for the purpose.

The drawing of the outlines, furthermore, is another source of error. This error was reduced, as previously explained, by using a plane-apochromatic objective practically eliminating the aberration. Even so, the drawing error amounted to 2.2% for both nuclei and 5.7% for the dorsal nucleus. The explanation of this difference seems obvious. As the dorsal nucleus is smaller and has a correspondingly smaller cross-sectional area, any deviation of the pencil while drawing is apt to result in greater relative difference between two small than between two greater areas.

As regards the planimetric error, this is fairly small, 0.9% for the whole nuclear complex as well as for the individual nuclei. Thus planimetry in these cases proved to be a relatively accurate procedure.

The combined effect of these three sources of errors, called the total methodological error, indicated by the coefficient of variation (page 72) is 4% for both nuclei and 7.6% for the dorsal nucleus separately. However, the variation within each group of the asphyxiated babies is greater (Table 14). These methodological errors only constitute a part of this variation, the greater part being due to other factors.

A relevant question in this connection is whether the prematurity in the majority of the cases may play a role.

Prematurity

Fuse (1913) appears to be the only one who has systematically investigated the morphogenesis of the cochlear nuclei Comparing the cochlear nuclei in an adult with a 5-month foetus, Fuse states

'Wie im Kapitel über die normale Anatomie des Ganglion ventrale [i e ventral cochlear nucleus] wiederholt erwähnt wurde, sind alle jene Einschaltungen grauer Substanz auch im gewachsenen Gehirn an genau den namlichen Stellen nachweisbar, wie beim 5 monatigen Fotus, nur mit dem Unterschied, dass beim Erwachsenen selbstverständlich die graue Substanz und vor allem die Nervenzellen viel reicher ausgebaut und entwickelt und wesentlich voluminoser sind' (op cit, p 162)

This statement may be interpreted in favour of the view that the cochlear nuclei in man at the developmental stage of 5 months have acquired their definite number of neurons

The findings in the present investigation lend support to this assumption It is shown that at least in babies 1–1½ months premature the number of nerve cells is of the same order of magnitude as found in the new-born Thus the control case No 51, 1 month and 9 days premature, which lived for only 35 minutes had 100,200 cells in the cochlear nuclei The control case No 15, 14 days premature, stillborn, had 96,000 cells, and case No 54, 1 1½ months premature, asphyxiated for 4 hours had 95,300 cells

The mean number of cells in the 9 control cases was 96,400 (Table 4)

However, the material includes 17 cases with a prematurity of more than 2 months Babies that much premature are nearly always asphyxiated, and no 'normal' control case could be obtained It may therefore be objected that in these highly premature cases the cochlear nuclei might still be immature with regard to the number of nerve cells No conclusive argument to the contrary is available However, it may be appropriate to point out that within this group of highly premature cases there are two specimens (Nos 32 and 40) where — in spite of preceding asphyxia of 6 to 12 hours — the number of nerve cells in the cochlear nuclei is almost 80,000, i e close to the lower limit of the normal variation (see cases 15 and 57, Table 4)

On the basis of the foregoing it seems permissible to conclude that in the group of less than 1½ months' prematurity the cochlear nuclei have acquired the mature number of cells As regards the more premature cases the evidence is inconclusive, but there is reason to assume that immaturity does not alone explain the low cell counts in these cases

It seems permissible, therefore, to rule out immaturity as a source of error of such magnitude as to derogate the validity of the findings

It may be maintained that the cellular changes and the loss of nerve cells observed in the cochlear nuclei are not satisfactorily explained by methodological errors, or by prematurity One may ask then Of what nature are these cellular changes?

The nature of the cellular changes

The cellular changes in all the cases appeared to be qualitatively similar, although the intensity differed considerably

The picture presented many points of resemblance to the severe cell change of Nissl, but vacuolization of the cytoplasm formed a more conspicuous feature

Similar pathological alterations are described by Kornyey (1954) as 'anoxisch-vasalen' cell changes Kornyey also mentions the vacuolization of the cytoplasm seen in cases corresponding to Nissl's severe cell change He stresses that both the ischaemic and the homogenizing cell changes described by Spielmeyer (1922) are anoxic in origin In his opinion it is permissible to speak of both morphologically as ischaemic-homogenizing cell diseases (anoxische Zellerkrankung) the presence of which should definitely indicate a hypoxic etiology

Cammermeyer (1958), surveying the literature, supports this view, and states that the anoxic nature of the neuronal changes is beyond doubt

In animal experiments cell changes similar to those encountered in man are reproduced by interfering with blood circulation in various ways (Gildea and Cobb 1930, Tureen 1936, Chornvak 1938, Weinberger *et al* 1940, Windle *et al* 1944, 1962, Courville 1953, Windle 1961, 1963 a, b)

The literature quoted definitely favours the conclusion that the cellular changes observed in the cochlear nuclei of the present series are due to asphyxia, which in all probability also explains the loss of nerve cells in these nuclei

However, in several of the cases other possible etiologic factors were present, the influence of which deserves further consideration

a) Intrauterine asphyxia

In calculating the asphyxiation time the possibility of a preceding period of intrauterine asphyxia presumably represents a factor, the role of which escapes definite control In 18 cases of the present series the case histories report irregularities Haemorrhage 9 cases, extended duration of birth, 3 cases, transverse position with narcosis 3 cases, and among the remaining one had a placenta praevia, one a greenish amniotic fluid and the last one a trauma during pregnancy, indicating the possibility of intrauterine asphyxia

Comparing these cases, grouped according to asphyxiation time, with the remaining cases no significant difference was found with regard to the number of nerve cells in the cochlear nuclei Therefore the opinion is ventured that whatever episodes of asphyxia may have occurred in utero prior to delivery, they *do not* seem to have influenced materially the findings of the present study

b) Cerebral haemorrhage

In 18 instances in the present series a cerebral haemorrhage was found at autopsy The haemorrhage was submeningeal or intraventricular In one-half of the cases the haemorrhage was so massive as to render serious interference with the cerebral circulation probable

There is a common tendency nowadays to ascribe a neonatal cerebral haemorrhage not only to mechanical influences, but to vascular lesions caused by deficient tissue gas exchange This leads to the concept of the anoxic condition as an important etiological factor in cerebral haemorrhage (Schwartz 1961) However, this is still a moot point Windle (1963a) is inclined to consider the leakage of blood into the cerebral tissues to be usually related to some kind of trauma, or to represent a terminal agonal artifact

Whatever the etiology, asphyctic or traumatic, the consequences of a haemorrhage will be a lowered oxygen supply and an aggravation of the asphyctic condition

In four of the control cases, a cerebral haemorrhage was found Three of these were involved in traffic accidents and died almost instantly The fourth was a premature child which lived for only 35 minutes The haemorrhage in these cases was of so short duration that it could not possibly have caused any loss of cells

c) Haemolytic disease

Not only the anoxia, but also the action of bilirubin as in kernicterus, and Rhesus iso-immunization represent problems relevant to this investigation

It is not agreed whether kernicterus represents an asphyxial sequela or should be considered as a special disease causing cell destruction It is explained by some authors as a result of increased permeability of the nerve cells to bile pigment following the damaging effect of oxygen deficiency (Aidin *et al* 1950) Govan and Scott (1953), finding the same histological picture in anoxic premature children with or without kernicterus, also support the theory that the oxygen deficiency is the primary factor In both anoxia and kernicterus a loss of hearing for high frequencies has been found (Crabtree and Gerrard 1950, Fisch and Norman 1961)

The latter authors also found an extensive destruction of both cochlear nuclei in two cases which came to autopsy, while the organ of Corti appeared normal They are inclined, however, to regard a hyperbilirubinaemia as the primary factor in these cases, alone or combined with overdoses of Vitamin K, which, in its analogous form and given in large doses, exceeding 5 mg, may cause haemolysis in the new-born (Sundal 1963) However, Dodgson (1962) states that the exact mode of action of bilirubin as a cerebral toxin 'if such it is', has yet to be established

In this series there are three cases in which a Rhesus iso-immunization was possible, cases Nos 11, 18, and 27 Their mothers were Rhesus negative In cases Nos 11 and 27, however, no antibodies were found in the mothers' blood 5–6 weeks before birth at which time they might have appeared

Case No 11 had neither any icteric staining in the brain, nor cerebral haemorrhage It seems likely that this was not Rhesus iso-immunization, and therefore the case was not rejected from the asphyctic group

Case No 27 had a yellow stained liquor, a cerebral haemorrhage and a heart defect However, the yellow stained liquor was most likely due to the cerebral haemorrhage and kernicterus could be excluded as no antibodies were found earlier, there was no icteric staining of the brain, and the bilirubin concentration

was only 1 2 mg/100 ml two days before exitus In all probability the hypoxia and the respiratory distress, augmented by the heart defect, were the primary factors in producing a loss of cells in the cochlear nuclei

In case No 18 it was reported that the mother 'possibly' was Rh negative, and a slight icteric staining of the skin was found the day before death However, neither in this case was any icteric staining found in the brain, and a healthy colour of the skin was reported on the first day of life That leaves less than one day for accumulation of a toxic amount of bilirubin, which seems to be too short a time Unfortunately, the bilirubin concentration in these cases was not measured, because of their short lifetime, but one would presume that a high bilirubin concentration must prevail for more than a few hours or perhaps a day, in order to produce disintegration of nerve cells Bilirubin is a toxic agent, which may influence the cochlear nuclei as well as other sites in the brain, but even in a manifest hyperbilirubinaemia hypoxia plays an important role It is shown that in hypoxic and premature infants there is a deficient or delayed development of the enzyme glucuronyl transferase, which is necessary to form the non-toxic bilirubin-diglucuronide (Brown 1962)

In four more cases, Nos 24, 26, 28, and 48, icterus or a yellow stained liquor was found, but no Rhesus incompatibility In none of these cases was the bilirubin concentration examined In cases Nos 26 and 48, no icteric staining was found in the brain, and the staining of the liquor evidently was due to the haematoma found in these brains

In case No 24, the colour of the skin was normal for the first hours, then during the next days repeated attacks of asphyxia and cyanosis followed, and the baby died on the 4th day, developing a strong icterus during the last hours It does not seem likely that the bilirubin could have inflicted any great damage during that short time

In case No 28 icteric staining was found in the walls of the ventriculus septi pellucidi, and this was not due to any brain haemorrhage, nor to a Rhesus incompatibility This may indicate a developing kernicterus, but it seems unlikely that this alone should be responsible for the observed loss of cells

On comparing the cases (Nos 11, 18, 24, 27, 28) suspected of hyperbilirubinaemia belonging to the group asphyxiated for 1–2 days with the remaining six cases of the group, a difference of 10,000 cells was found between the average number of cells in the cochlear nuclei of these subgroups Although no definite conclusions can be drawn, this may indicate that hyperbilirubinaemia is a factor tending to increase the effect of the hypoxic condition, as maintained by Fisch (1962)

d) Mongolism

Case No 16 had hyperbilirubinaemia and, possibly, mongolism The Rhesus status of the mother had not been examined, but the child was of blood group O, Rh positive, and Coombs reaction was negative, which makes an iso-immunization improbable However, there was a slow rise in the bilirubin concentration to 14 2 mg 100 ml on the 4th day of life and an exchange transfusion was performed on that and the following day A slow decline of the bilirubin concentration

resulted, to 12 mg/100 ml on the 9th day On the 10th day it was 16 mg/100 ml and later it was not measured In this case it is a question whether the relatively high concentration of bilirubin had persisted long enough before exchange transfusion was done, to cause brain damage This seems unlikely, as the bilirubin levels on the preceding days were 12 4 and 7 mg/100 ml Nor is it reasonable to assume that the bilirubin levels on the days immediately following the transfusions had reached toxic values It may be recalled that the bilirubin tolerance increases rapidly within the first few days of life (Brown 1962)

The notes in the records regarding possible mongolism in this case also call for a short comment It is well known (see Benda 1949 and Jacob 1956 for references) that in mongolism the entire vascular system is hypoplastic Jacob mentions specifically the basilar artery This condition may represent a predisposing factor in connection with circulatory disturbances To what extent a possible hypoxia may be responsible for the neuropathological changes described in mongoloid brains remains an open question Benda however, states that 'edema of the nerve tissue with asphyxiation of the cells is one of the most important pathologic features It is therefore evident that the loss of ganglion cells in mongolism is due to a continuous dropping out of cells, owing to a pathologic condition of the brain The remaining nerve cells are in a stage of severe disease either ischemic or sclerotic, with all those changes described by Nissl Spielmeyer, Cobb and recent investigators of asphyxiation'

No references to the conditions of the cochlear nuclei in mongoloid brains have been found in the literature, but the heavy loss of cells found in the present case (42 300 cells) may well represent the effect of asphyxia

The selective vulnerability of the cochlear nuclei

The loss of hearing so frequently observed in cases surviving a period of neonatal asphyxia deserves further comment. In the first place one may ask whether the prevalence of this symptom in the symptomatology of the postasphyctic state is an expression of selective vulnerability of the auditory system, or merely reflects the fact that for obvious reasons disturbances of hearing are comparatively easily detected

The hearing losses found after neonatal asphyxia are already audiometrically registered in pre school children at which time other neurological manifestations may be more easily overlooked

The present investigation points out the cochlear nuclei as the site of particularly striking changes, which naturally prompts the question of a possible selective vulnerability of these nuclei The state of asphyxia entails a deficient oxygen supply to the tissues Highly vascularized tissues presumably suffer most under conditions of asphyxia

As emphasized by Courville (1952) a region with high metabolism is apt to suffer more and show damage more quickly under asphyctic conditions than metabolically less active regions

In his comprehensive studies of the vascularization of the brain Craigie (1937) found that the nuclei in question, more specifically the dorsal cochlear nuclei, represent the most richly vascularized areas of the brain stem Craigie's conclusions are based on studies of lower mammals, but there is reason for assuming that the conditions in man are similar in principle This abundant vascularization and the high metabolic rate presumably related to it might well explain the apparent high vulnerability of the cochlear nuclei

The rich vascularization presumably should imply a correspondingly ample blood flow to the cochlear nuclei The recent investigation of Kety (1963), however, does not quite corroborate the conclusions drawn on the basis of the vascular pattern Using diffusible indicator substances Kety measured the local blood flow in various parts of the brain and found that the inferior colliculi topped the list in this respect The geniculate bodies, the auditory and sensory motor cortex came next, while the blood flow of the cochlear and vestibular nuclei did not amount to more than half of that of the inferior colliculi Kety's investigations point to a generally high blood flow through all subdivisions of the auditory system, especially at midbrain and cortical levels These findings are of particular interest in connection with the observations of Windle (1961) and Windle *et al* (1962) who in asphyxiated monkeys repeatedly found degenerations in the inferior colliculi, and in a severely asphyxiated monkey estimated the neuronal loss at about 50 per cent

The present observations in human material tend to support the findings of Windle No counting of cells was performed in the inferior colliculi, but in some cases cells were observed showing degenerations, similar to those found in the cochlear nuclei Thus it may well be that the vulnerability to asphyxia is common to both of these auditory relay nuclei The discrepancies in the various findings may be due, partly or entirely, to species differences, Craigie's investigations being based on rats, those of Windle and Kety on monkeys and cats, and the present ones on human material and kittens For the time being the question of a specific vulnerability must be left open

The fact remains that in the present series the cochlear nuclei have suffered a loss of cells, more pronounced in the dorsal than in the ventral nucleus The etiology is presumably the lowered oxygen supply to a highly vascularized region In this connection it is of interest to consider whether these pathological findings are also consistent with the clinical picture encountered in cases with neonatal asphyxia and a subsequent loss of hearing

Clinical findings

Clinical investigators, among others Fisch (1956) and Flottorp *et al* (1957) point out the loss of high pitch sensitivity following neonatal asphyxia However, they disagree with regard to the probable localization of the damage within the auditory system Fisch, supported by Barr and Klockhoff (1959), assumes that the pathological changes are situated within the dorsal cochlear nucleus where

the high frequencies are presumably relayed Flottorp *et al*, on the oth studying cases of athetosis following neonatal asphyxia, consider a co pairment to be the cause of hearing loss in these patients All these in base their conclusions on clinical evidence, which alone, i e without hi control, can hardly be conclusive However, the findings in the present tion lend support to the view advocated by Fisch In this connection it appropriate to consider the literature on the tonotopical organizati the auditory system

Tonotopical organization

It seems a well established fact that in the cochlea, the receptors for high tones are located in the basal coil (Crowe *et al* 1934, Culler 1935, Stevens *et al* 1935, Lewy and Kobrak 1936, Stevens and Davis 1938)

However, the neural projection of the basal coil on the primary acoustic nuclei remains a controversial question

Some investigators, e g Stotler (1949) and Rasmussen (1957), found no degenerated fibres in the dorsal cochlear nucleus after destruction of the cochlea The majority (Cajal 1909, Lorente de Nó 1933, Jungert 1958, Powell and Gowan 1962), however, agree that the dorsal cochlear nucleus receives primary fibres Galambos (1954) states that the cochlea is 'unrolled' in several if not in all of the 13 subdivisions of the cochlear nuclei, which include the dorsal nucleus and Rose *et al* (1959) claim that the frequency sensitive neurons are arranged from high to low in an essentially dorsoventral sequence

The more accurate projection of the basal coil of the cochlea is a point of controversy According to Lewy and Kobrak (op cit) and Rose *et al* (op cit) the basal coil of the cochlea projects on to the dorsal part of both nuclei Powell and Gowan (op cit) on the other hand, found a projection to the medial parts of the nuclei They point out, however, that their study was not systematic on this point, their aim being primarily to show that no primary fibres pass beyond the cochlear nuclei

Most of the experiments were performed on cats, and the results can only serve as indications of the tonotopical organization in man However, with due reservations taken for species variations, it seems reasonable to assume with our present knowledge, that lesions involving the dorsal parts of both nuclei in man are in all probability accompanied by a high tone loss

Thus the more recent reports have somewhat changed our concept of the tonotopical localization within the cochlear nuclei The earlier prevailing opinion that the fibres which carry high frequency impulses are concentrated in the dorsal nucleus must be modified accordingly The high frequency impulses are projected to the dorsal part of both nuclei The findings in the present investigation showing a particularly heavy loss of cells in the dorsal nucleus, but also a substantial loss of cells in the ventral nucleus, are compatible with this assumption

The relation between the loss of cells, asphyxiation time, and function

As regards the severity and duration of asphyxia the estimation of these factors in man must of necessity be approximate In the present series, the recorded time of onset and duration of each attack of asphyxia were used to calculate the total duration of asphyxia in hours As appears from Figure 18, the loss of cells increases roughly in proportion to the duration of asphyxia

During the initial 24 hours, the loss is most marked, whereafter the rate of loss apparently declines It was furthermore found, that the loss of nerve cells is manifest already after 5–7 hours of asphyxia (20 per cent reduction of the number of nerve cells in this group)

In order to control the reliability of these calculations, the cases were arranged in groups according to the exactly known lifetime of the babies The rate of loss of cells shows a strikingly similar pattern, as is evident from comparison of the graphic representations in Figure 18

The findings in the present cases were due to an asphyxia so severe that it was incompatible with survival It is extremely difficult to draw any conclusions about the conditions in surviving cases from these results It is highly probable, however, that in surviving cases less cells would be so severely affected as to disintegrate, and several of the remaining cells might well regenerate Romanova (1956) stated that brain cells are capable of recovery even after severe hypoxia, but Lindenberg (1963) states that as soon as vacuoles develop in a nerve cell, it will not regenerate It seems probable, however, that the massive loss of cells found in these fatal cases also indicates a loss of function in surviving cases However, reservations must be made on this point, because of our insufficient knowledge of the function of the cochlear nuclei Only scanty data are available

Lorente de No (1933) has demonstrated their complicated structure Galambos (1954) has shown that a particular frequency evidently produces excitation in some cells, inhibition in others, and no change whatever in still others The present investigation shows that the cochlear nuclei normally contain about 100,000 cells This is about 4 times as many as there are hair cells or ganglion cells in the cochlea Some of the cells are short, accessory neurons, whose axones remain entirely within the cochlear nuclei, and these give almost limitless opportunities for interconnection and interplay between the various fibres, possibly discriminating the stimuli It seems reasonable to assume that a substantial loss of cells in these nuclei will seriously affect the hearing, not only for pure tones, but also for more complicated auditory functions such as the interpretation of speech

However we possess so little information about the function of the cochlear nuclei that at present no reliable conclusions can be drawn

The experimental material

New born kittens did not show any pathological changes in their cochleae and new born or premature kittens did not show any loss of cells in their cochlear nuclei

Among the experimental investigations performed previously some authors report degenerations in the central nervous system and some do not Examining their methods, we find that those employing a total circulatory arrest (Gildea and Cobb 1930, Tureen 1936, Weinberger *et al* 1940, Windle *et al* 1944) found changes in the nerve cells, but those employing oxygen deficient air mixtures or tracheal clamping (Ford 1928, Chornyak 1938, Thorner and Lewy 1940, Lawrence and Wever 1952, Gulick 1958, Falbe-Hansen *et al* 1958, Windle 1961) refer to a variety of findings, from completely negative to severe cell changes

It seems obvious that the results largely depend on three factors the percentage of oxygen inspired, the duration of each exposure, and the survival time In addition, the age of the experimental animals must be taken into consideration Before starting the experiments in the present series, all these factors were considered The 4 % oxygen mixture was chosen on the basis of the experiences of previous investigators Ford had his kittens living in an atmosphere of 5 5 6% oxygen for 12 hours, and after 0–2 weeks survival time found no microscopic changes in their brains On the other hand, Gulick found that his cats did not tolerate a 3 % oxygen mixture very well, he had to perform artificial respiration on some of them after only one minute Therefore, the optimal mixture for the present purpose seemed to be 4% oxygen A 4% oxygen mixture gives a partial tension of one fifth of the normal, or lower than 30 mm Hg in the lungs of the kittens, when the physiological dead space is taken into consideration In premature asphyxiated babies Blystad (1956) found that the oxygen tension of cutaneous blood varied between 15 7 and 47 2 mm Hg, with a mean value of 29 06 mm Hg Thus, kittens exposed to a 4 % oxygen mixture will have about the same oxygen tension in their lungs as the asphyxiated babies under investigation

In Table 9 the only positive findings in these experiments are shown the volume of the cochlear nuclei was less in every age-group of the asphyxiated kittens compared to the controls

As to the duration of the total exposure it varied from 45 minutes to 18¾ hours, distributed over 6 days (Table 2) However, the single daily exposure was maximally 6 hours, as the kittens were then on the point of suffocation Each exposure was carried out until their respiration failed This is comparable to the respiration failure in the human babies, but it is remarkable that some of the latter showed a loss of cells after only 5 hours of asphyxia, and the kittens did not

However, Windle (1961) immersing new-born and young monkeys in an atmosphere of pure nitrogen did not find any changes in the nerve cells because 'Cardiac depression occurred so rapidly in the newborn that the animals did

not survive long enough for structural changes to manifest themselves in the nervous tissue'

It is probable that the same was true of these kittens, and that this way of experimentation will not lead to visible degenerations in the central nervous system The reason is that after some hours exposure, the circulation becomes deficient, the animal has to be taken out and the nerve cells recover before another exposure can take place

It is seen in Table 2 that only in a few cases was the single exposure as long as 5–6 hours Mostly it varied between ½–3 hours and, given time in between for recovery, the nerve cells seemed able to endure several such periods As regards the premature kittens these did not live long enough for degenerations of the nerve cells to develop The chief aim of this particular experiment, however, was to see whether the cochlear nuclei in premature kittens contained the same number of cells as in the new-born kittens Only in one premature kitten, which survived for 2 days and 8 hours and spent 2½ hours in the 4% oxygen mixture could a loss of cells have been expected As this did not occur, it seems reasonable to assume that the intermittent gasps provided enough oxygen for the nerve cells of so premature a kitten, even during the 2½ experimental hours

Whether this or some other unknown factor helped to preserve the nerve cells in the other kittens cannot be determined In any case the nerve cells in the cochlear nuclei of premature kittens and the sensory cells of the cochlea in new-born and young kittens tolerate hypoxic conditions far better than those of human premature babies

GENERAL CONSIDERATIONS

The role of asphyxia in the etiology of neurological defects in the new born is steadily becoming clearer

It is now considered a well established fact that asphyxia is responsible for a number of neurological and psychological disorders during childhood, from severe mental disorders (e g Schreiber 1938, Courville 1953, Morstad and Kaada 1953 Skatvedt 1958) to minor forms of behavioural or intellectual impairment (e g Darke 1944 Morstad 1953 Bailey 1958)

The increasing knowledge of the somatotopical organization of the brain has added materially to the understanding of the effects of asphyxia Degenerative changes have been previously demonstrated in different brain structures (see for references Cammermeyer and Adams 1954 Cammermeyer 1958) With our clinical knowledge of a loss of hearing predominantly for the high tones (Fisch 1956) and also of the general susceptibility of nerve cells to asphyxia (Spielmeyer 1922, Kornyey 1934 1954) degenerations in the central auditory pathways might be

expected after asphyxia the more so, as the cochlear [illegible] highly vascularized and thus very susceptible (Craigie 1937, [illegible]

However, other parts of the auditory pathways are [illegible] able Thus Windle (1961) in his material of monkeys, found [illegible] inferior colliculi most commonly damaged In this study, the [illegible] ination (Hall 1962 1963) of various regions of the brain [illegible] superior olives, the Purkinje cells of the cerebellum and [illegible] The initial intention was to investigate the entire auditory [illegible] became clear that a limitation of the task was necessary The [illegible] observed in the cochlear nuclei called for particular [illegible] investigators (Fisch 1956 Flottorp *et al* 1957, Barr and [illegible] with regard to cochlear impairment after asphyxia it [illegible] examine also the organ of Corti

The massive loss of cells found in the cochlear nuclei of the [illegible] lends support to the view advocated by Fisch (op cit) and [illegible] who point to a central damage, whereas the finding of smaller [illegible] changes in the peripheral sense organ indicates that the [illegible] probably is of secondary significance At all events the [illegible] that neonatal asphyxia in all probability is the etiologic [illegible] in more cases than hitherto recognized The full importance [illegible] asphyxia is still open to discussion It is highly probable [illegible] is one of the primary factors in several diseases occurring [illegible] diseases which are also represented in this material [illegible] this view concerning mongolism On the basis of the [illegible] Gerrard (1950) F [illegible] to assume that [illegible] probably the sam [illegible] processes of the cell

It is evident that the supply of oxygen may also be impaired [illegible] rhage which was found in 18 instances in the present series [illegible] cases of intrauterine asphyxia The extent of asphyxial damage [illegible] of the brain is dependent upon its metabolic rate (Courville [illegible]) to be high in the cochlear nuclei the capillary density of which seems (Craigie 1937) [illegible] very great

Summing up this material seems fully to support the [illegible] advocated by Fisch in a personal communication (1962)

In some circumstances and mainly during a definite stage of development of the central nervous system in the perinatal period, the metabolism of this part is higher than of any other part of the central nervous system During this period the cochlear nuclei can be selectively damaged by any agent which may interfere with the high metabolic needs of the [illegible]

SUMMARY

The purpose of the present investigation was

1 To examine histologically the pathological changes in fatal cases of asphyxia neonatorum, with particular reference to the organ of Corti and the cochlear nuclei

2 To demonstrate the quality and the quantity of these changes

3 To evaluate whether the changes observed might reasonably explain the loss of hearing found in surviving cases

Sixty human brains and 94 of the corresponding temporal bones were collected For supplementary experiments 62 kittens were used Severe asphyxiation was induced by immersion in a gas mixture of 96% N_2 and 4% O_2 This was carried out to the point of suffocation, in some instances for several consecutive days For various reasons some of the material proved unsuitable for histological examination and was excluded, leaving

49 human temporal bones
31 temporal bones of kittens
41 series of the cochlear nuclei from the human cases of asphyxia neonatorum
62 series of the cochlear nuclei from normal and asphyxiated kittens

The cochlea

The organ of Corti appeared normal in 13 of the human cases and in 11 cases only slight changes were visible

The rest of the material showed more pronounced defects, in the author's opinion owing to a failure in the technical procedure In the kittens, including the controls changes of various degrees were observed in 21 organs of Corti, all of which were deemed to be of an artificial nature In 10 cases the organ of Corti appeared entirely free of changes

The cochlear nuclei

in the human material showed qualitative as well as quantitative changes The qualitative changes were characterized by degenerations, ranging from blurring of the contours of the nerve cells and peripheral displacement of the nucleus to vacuolization of the cytoplasm loss of the nucleus and total disintegration These changes prompted a quantitative examination of the cochlear nuclei A method for counting the number of nerve cells was devised, and yielded the following

results in the human control material the average number of cells in the cochlear nuclei was 96,400, ranging from 87,700 to 112,500 The asphyxiated cases were arranged in four groups according to their asphyxiation time 0–10 hours, 10–24 hours, 1–2 days, and more than two days The average number of cells in the cochlear nuclei of these groups was 76,500, 58,300, 51,700 and 52,700 respectively, which corresponds to a loss of cells varying, according to the groups, from 20 to 45 per cent, evidently roughly correlated to the duration of the asphyxia

The dorsal cochlear nucleus was more heavily affected than the ventral In the control cases the dorsal cochlear nucleus contained 25,400 cells In the asphyxiated cases the numbers ranged from 16,300 down to 8,700, corresponding to a loss of from 36 to 66 per cent of the cell population

In the experimental material of kittens no loss of nerve cells could be demonstrated in the cochlear nuclei

The investigation favours the view that neonatal asphyxia plays an important etiological role in congenital nerve deafness

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Acta

ACTA OTO-LARYNGOLOGICA

SUPPLEMENTUM 195

FINNISH OESOPHAGEAL SPEECH AFTER LARYNGECTOMY

Sound spectrographic and cineradiographic studies

BY

JYRKI KYTTÄ

ACTA OTO-LARYNGOLOGICA · KAROLINSKA SJUKHUSET, STOCKHOLM 60

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COVER

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CORRIGENDA

P. 9, third chapter, line 6 *for* diffecult *read* difficult

P 15, third chapter, line 7 *for* (1958) *read* (1952)

P 19, first chapter, line 1 *for* F 2 *read* F 2,

P 27, Table 3, line 1 *for* always the *read* always on the

P 29, third chapter, line 2 *for* speakers the vibration of the fundamental tone or subglottis, viz. the frequency *read* speakers the frequency of the vibration of the fundamental tone

P 33, first chapter, line 4 *for* (Fig 2) *read* (Fig 3)

P 33, Table 5, line 11 *for* *y* 295 • 276 *read* *y* 295 276

P 33, Table 6,

for	Vowels	u	o	a	ä	e	i	y	ö	
	F1	570 0	641.5	*414.0*	*555.0*	686.5	*402.5*	598 0	*427.5*	cps
	F2	*444.0*	*485.5*	*556.5*	*514.0*	*444.5*	*382.1*	*562.0*	*372 0*	»
	F3	629.5	571.5	665.5	632.5	*372 0*	*401.5*	*482.5*	*536 6*	»
read	Vowels	u	o	a	ä	e	i	y	ö	
	F1	570 0	641.5	414 0	555 0	686.5	402.5	598 0	427.5	cps
	F2	444 0	485.5	556.5	514 0	444.5	382.1	562.0	372 0	»
	F3	629.5	571.5	665.5	632.5	372 0	401.5	482.5	536 6	»

P 37, line 1 from bottom *for* vowel e, *read* vowel e and y,

P 45, second chapter, line 2 *for* *i, e, y, ä, ö* *read* *i, e, y, ö, ä*

P 46, fourth chapter, line 1 *for* semiovowel *read* semivowel

P 47, Fig 17, line 3 *for* of the controls *read* of u and i

P 53, second chapter, line 7 *for* F 1 of *a* *read* F 1 of *u*

P 56, second chapter from bottom, line 2 *for* 6—8 secs *read* 0.1 sec

P 65, second chapter, line 1 *for* 1—2 secs. *read* 0.1—0.2 sec

P 79, third chapter, line 1 *for* *u*, *o* and *e* *read* *u*, *o*, *e* and *y*

P 79 fourth chapter, line 4

for	F 1	*a*	*ä*	*i*	*y*	*ö*
read	F 1	*a*	*ä*	*i*		*o*

P 79, fifth chapter, line 3 *for* *u*, *o* and *e* *read* *u*, *o*, *e* and *y*

P 88, third chapter, line 6 *for* *u*, *o* and *e* *read* *u*, *o*, *e* and *y*

P 94, *for* Winckel, E., 1958 Elektroakustische Untersuchungen *Folia phoniat (Basel)*, *4*, 1952 *read* Winckel, E., 1952 Elektroakustische Untersuchungen. *Folia phoniat* *4*, 93

FROM THE OTO-LARYNGOLOGICAL CLINIC
(HEAD PROF. OTTO H. MEURMAN M.D.)
OF THE UNIVERSITY OF TURKU FINLAND

ACTA OTO-LARYNGOLOGICA

SUPPLEMENTUM 195

FINNISH OESOPHAGEAL SPEECH AFTER LARYNGECTOMY

SOUND SPECTROGRAPHIC AND CINERADIOGRAPHIC STUDIES

BY

JYRKI KYTTA

VAMMALA 1964

Vammala 1964
Vammalan Kirjapaino Oy

To the memory of my Father

CONTENTS

PREFACE

My deep gratitude is extended to my Chief Prof Otto H. Meurman, M D, Head of the Oto-laryngological Clinic of the University of Turku, for the great interest he has shown throughout my investigations, as well as for encouragement, advice and many valuable suggestions

I am greatly indebted to Prof Tauno Palva, M D, Head of the Oto-laryngological Clinic of the University of Oulu, for helpful discussions and criticism which, during the progress of my work, revealed new aspects of the subject of my investigation

I should also like to thank Prof Antti Sovijarvi, Ph D, Head of the Department of Phonetics, University of Helsinki, who reviewed my manuscript, and without sparing time and trouble, helped to widen my views on Finnish phonetics in general and on questions related to this study in particular Mr Kalevi Wiik, Ph L, has also given valuable help on various phonetic matters and questions of English phonetic terminology which I gratefully acknowledge

I take this opportunity to thank my former teacher and Chief, Prof Urpo Siirala, M D, Head of the Oto-laryngological Clinic of the University of Helsinki, and Mrs Sirkka Siirala, M L, Phoniatrist of the Department of Speech Disorders of the same Clinic, for their help in the selection and examination of the test subjects

My thanks are also due to Dr Erkki Sysimetsa, M L, who performed the cineradiographic studies included in this research at the Cardiorespiratory Research Unit of the University of Turku, to Mr P Aaltola, Ph M, for the treatment of statistical problems, to Mrs Aili Ryynanen, Ph M, Librarian of the Faculty of Medicine, University of Turku, for her help in assembling the literature, and to Miss Aino Wuolle, Ph. M, who translated my manuscript into English.

Turku, October 1964

Jyrki Kytta

CHAPTER I

INTRODUCTION. PURPOSE OF THE INVESTIGATION

The incidence of cancer of the larynx, most frequently attacking patients in the age range 50—60 years, represents about 4 per cent of all malignant human tumours (Gatewood 1945, Montreuil 1956, Saxén & Hakama 1964). The proportion of women in the total has been variously reported, with a maximum of 6 per cent (Meurman 1953, Vaheri 1956, Kleinsasser 1961, Lauerma & Siirala 1962)

When the degree of severity of the cancer necessitates total laryngectomy, this invariably entails loss of speech, the most important medium of human communication The best compensation for this loss is oesophageal speech Seeman was the first to adopt this term in 1920 for the technique which in about 70 per cent of all cases results in satisfactory voice and speech without any artificial devices Air trapped in the upper part of the oesophagus is forced into the hypopharynx through the oesophageal orifice closed by the cricopharyngeal sphincter (pseudoglottis), it is the pseudoglottis which — as a rough substitute of the larynx — provides the oesophageal voice with its fundamental frequency and pitch

Studies of the mechanism involved in the voice production of laryngectomized subjects since the 1920's have focussed mainly on anatomic-physiological aspects because of the advent of roentgenological facilities Phonetically, however, the patients have been evaluated mainly on the basis of acoustic observation, since assisting technical devices, serving to bring out various details of phonation, have been on a modest scale and also diffecult to operate In the 1940's, through the introduction of automatic »Visible Speech» devices, the Sonalator and especially the Sonagraph, entirely new facilities became available for the analysis of oesophageal speech too To the present writer's knowledge laryngectomized patients have not hitherto been thus studied in regard to all sounds of any spoken standard language

By supplementing sonagraphic investigation with cineradiography it has proved possible to obtain a clearer anatomic-physiological picture of the function of the pseudoglottis The radiation effect in these cineradiographic studies could be reduced by synchronizing the roentgen generator and the shutter of the camera

It is the purpose of the present work to study the oesophageal speech of laryngectomized individuals keeping the following points in view

(1) The fundamental pitch of oesophageal speech and the factors influencing it

(2) The vowel formant structure of oesophageal speech, and the formant intensities as compared with each other

(3) The acoustic qualities of consonants in oesophageal speech

(4) The site and shape of the pseudoglottis and the part played by it in the fundamental pitch of oesophageal speech

EARLIER INVESTIGATIONS

The first case on record of a patient who attempted using oesophageal speech of a kind, on account of laryngeal obstruction due to trauma, was from the early part of the 19th century. In 1828 Raprand mentioned such a case before the Academie des Sciences in Paris. Nearly three decades later Bourguet (1856) reported on a similar case, and so did Czermak (1859) and Seiler (1888).

At that time operation aimed at maintaining a permanent communication between the trachea and the pharynx with the aid of the Czerny-Gussenbauer artificial larynx, or speech cannula, which was used as a means of compensating for the lost voice producing activity of the vocal cords (Czerny 1870, Gussenbauer 1874). When the Berlin surgeon Gluck somewhat later (1881) radically altered the surgical principles by separating the trachea from the pharynx, the above design of artificial larynx was gradually discarded. Gluck called attention to the importance of oesophageal speech, suggesting that it may also be termed »voix éructante». Many investigators found to their surprise that it was possible for laryngectomees to speak by this method also (Strübing 1888, Solis-Cohen 1893).

Schmidt (1888) presented a patient, in his opinion an example of almost complete speech rehabilitation, who spoke without an artificial larynx using what Landois termed a »Pseudostimme». Both Landois and his colleague Strubing 1889 assumed that the pseudoglottis was located between the tongue and the palate and thought it well possible for the top of the oesophagus to serve as an air reservoir. Fränkel (1893) assumed that the oesophageal air could cause the pharyngeal mucosal folds — a kind of »glottis spuria» — to vibrate, thus producing pharyngeal voice.

At the first international Congress on Laryngology in Vienna 1908 Gutzmann presented a series of 25 laryngectomized patients, who had all learned to speak again. It is evident that interest was now increasing in speech re-education after laryngectomy. The name of Gottstein — outstanding in speech therapy — also belongs to this time period, half a century back.

Since Seeman (1920) had demonstrated that the actual air reservoir was the oesophagus, the designation »stomach voice», advocated by many, was gradually abandoned and superseded by the term oesophageal voice, or oesophago-pharyngeal voice, which is now well established. In the nineteen-twenties, when interest in the [illegible] was at its height in various West-European countries, [illegible] other

Seeman who carried out basic research in the field of phonetics and pathologic physiology (e g Dahmann 1924, Voorhoeve 1926, Pratje 1926, Schilling 1927, Stern 1929)

Dahmann was able to show roentgenologically with the aid of oesophageal probes that active contraction occurred during phonation in laryngectomees and Seeman (1926) with similar instruments that the contraction was most active in the upper third of the oesophagus Pratje, who studied the anatomic-physiological function of the oesophagus using *Hasselwander's* stereoscopic x-ray device, only found negligible movement in connection with respiration and phonation Such a remarkable difference in results is probably explained by the fact that this latter method is purely roentgenological

In Voorhoeve's view the stomach acted as air reservoir during speaking and it was possible to control the air by opening and closing the cardia at will At that time there was a heated controversy between Gutzmann and Stern as to whether the stomach really played a part in oesophageal speech (Stern's opinion) or not This disagreement lasted for years and was *finally solved by establishing that in beginners the stomach may co-operate*, whereas in trained speakers it is only the oesophagus that fills with air (Beck 1931) As late as twenty years afterwards numerous investigators have been studying the part played by the stomach in oesophageal speech showing convincingly that no speech promoting opening movements occur at the cardia (Cojazzi 1950 Luchsinger 1952, Pommez 1953, Schlosshauer & Mockel 1954 Beck 1956)

Some researchers have even questioned the role of the oesophagus in the speech of laryngectomees and state, contrary to the majority, that the *air reservoir forms in the hypopharynx* whereas the oesophageal air serves only as reserve air of a kind (Pelegrini & Ragaglini 1951, Schlorhaufer 1955) Beck distinguishes two types of voice in laryngectomized subjects the oesophageal voice and the pharyngeal one In the latter the air reservoir would reside in the hypopharyngeal cavity

Goto and his co-workers (1960) found that the intake of air in oesophageal speech is either inspiratory or deglutitory It was observed by *roentgenological examination that the oesophagus is inflated with air simultaneously* in its full length in the inspiratory type while in the deglutitory type only the upper part of the oesophagus is inflated, especially in the early stage of development of oesophageal speech

The co-ordination between respiration and voluntary air-expulsion during oesophageal speech has also been studied According to Burger & Kaiser (1925) voice production in laryngectomees naturally enough occurs during expiration *The same result was reached later by Bateman 1953, Di Carlo* et al 1955 Damste 1958 and Levin 1962

Stern and Denes (1938) noted that the site of the pseudoglottis was irregular a pseudoglottis may develop at any place where a mucosal fold scars or muscles cause narrowing Perello (1953) has stated that there are seven areas where a pseudoglottis may form the uppermost

is the ridge of the tongue and the lowermost is the middle of the oesophagus These variations in the anatomy of laryngectomized speech are reminiscent of Kallen's observation that »every fold of mucous membrane, every favorably placed cicatricial band, every muscle or muscular remnant may serve as the basis for the development of a pseudoglottis» (Kirchner et al 1963)

Studies of the location and mechanism of the pseudoglottis have been carried out by Lindsay et al (1944), Moolenaar-Bijl (1953), Brankel 1954, Hoople & Brever (1954), Mockel & Schlosshauer (1955), Vandor (1955), Di Carlo et al, van der Berg (1956), Schwab (1957), Damsté (1957, -58, -59), Weichs (1958), Motta et al (1959), Goto et al, Bohme & Schneider (1960), Fumeaux (1961), Černoch & Žobril (1961), and Kirchner et al These investigators have analysed the speech production mechanism of good oesophageal speakers with the aid of roentgen tomography and cineroentgenography and measured the pressure variations in the pharynx and oesophagus during phonation The pseudoglottis was usually found to lie in the lower portion of the hypopharynx and in the area of the oesophageal orifice, at the level of approximately the 5th or 6th cervical vertebra The above workers also showed that the air required for phonation is trapped in the upper part of the oesophagus and, when expelled, vibrates the pseudoglottis Poor speakers, with a bubbling, mucous voice, were found to have the largest hypopharyngeal lumina (Kirchner et al)

Other factors were variable among both good and poor speakers whether the cricopharyngeus was at C VI, C V or C IV, whether the pseudoglottis consisted of a thin band or a broadly based mass, the length of the vibrating segments, the tonus or flaccidity at the cricopharyngeus as measured by pressure studies All varieties of these were found in good and in poor speakers (Černoch & Žobril, Kirchner et al)

Wedler & Schwab (1955) made a roentgenographic study of anatomical and functional changes in the hypopharynx after laryngectomy The cicatricial changes seen in the walls of the hypopharynx did not appreciably interfere with the contractile movements associated with swallowing There were small functional disturbances the slower-than normal passage of food and the slight accumulation of opaque medium frequently observed at the oesophageal orifice, which necessitates a new swallowing movement

The relationship between the type of operation and the quality of the oesophageal voice was studied by Robe et al. (1956) They were unable to demonstrate any definite correlation between voice quality and the procedures performed, notably in the case of removal as compared with preservation of the prelaryngeal muscles or pharyngeal wall Most investigators have consistently reached the opposite result Among other workers Negus (1938), Tarneaud (1948), Levin (1952), Hodson & Oswald (1958), and Sercer (1959) hold the view that the ability to acquire the oesophageal voice and its quality are directly related to the extent of the surgical trauma Skeletonization of the larynx must be performed with extreme caution, taking care that the extralaryngeal muscles, especially the

cricopharyngeal musculature and nerves, are injured as little as possible Damsté (1959) calls attention to closure of the pharynx, since lacking caution in suturation may result in, among other things a diverticulum in the anterior pharyngeal wall which is an irreversible lesion

Studies of the speech mechanism of laryngectomized subjects since the 1920's have centred chiefly upon the anatomic physiological function of the oesophagus, if only because of the available x ray facilities Phonetic studies have mostly been based on acoustic observation alone, since accessory apparatuses, serving to clarify the various details of phonation, have been difficult to use Thanks to advances of electroacoustics, however, apparatus gradually evolved with which reliable and quicker analysis of oesophageal speech is possible

The kymograph had various accessory parts, such as a mouth funnel, a laryngeal capsule and a nasal olive, to which styluses were attached for registering voice quality on sooted paper This device and a more highly developed type, the electrokymograph, were gradually oustedt by other methods e g Fourier analysis developed by the Munich physiologist O Frank, whose device became known as the Frank apparatus The analysis however, concerned only low frequencies The oscillograph (Braun's tube) was later introduced in it the movements of an oscillating point are photographed and an oscillogram is thus obtained, further, a seeker tone analyser (Suchtonanalysator) and an automatic recorder of intonation, which constructs an amplitude curve taking account of even the smallest voice variations The seeker-tone analyser has made possible the study of also weaker sound components because the amplification of the sound passing through the filter or seeker-tone, can be graded if desired

By using these instrumental methods the investigators already mentioned, *Gottstein Gutzmann Seeman Stern Schilling Beck, Luchsinger, Burger &* Kaiser and Brankel have studied the structure of in most cases, sustained vowels and consonants It was demonstrated that the slight operative alteration has also affected the vowels to some extent, and their lowest two energy stress areas or formants could generally be identified More intensity was found to be located in the upper frequency areas than in the normal speech range In some cases a change of vowels was found on acoustic observation in such a way that *a* resembled *o* or *u*, while *e* tended to be like *i* As far as consonants are concerned, those requiring much air and those producing only little acoustic effect in relation to air expenditure (the nasals) were found to be the most difficult to phonate Occasionally voiced phonemes could also change into their unvoiced counterparts when the economical use of the small quantity of available air was difficult

However the examination facilities briefly described above and some other similar methods are extremely time-consuming and difficult As already stated new possibilities emerged in sound quality analysis as a result of the introduction of two »Visible Speech« devices the Sonagraph and

the Sonalator, which are automatic speech analysers designed by the Bell Telephone Laboratories The former of these was used in the present study, so it will be dealt with in greater detail later (Chapter IV) The Sonalator, in which the subject being tested sees his own speech oscillographically as a continuous curve for 4 seconds, can be used with success to make speech therapy more graphic in cases of voice and speech disorder and also in post laryngectomy patients

Sonagraph studies have so far been made to a very small extent for the purpose of throwing light on the physical characteristics of oesophageal speech Among the first to study this question were Tato et al (1954), who directed chief attention to the fundamental frequency of oesophageal speech and found it to be 30—60 cps after laryngectomy at the early stage of oesophageal voice development, but to increase to 60—150 cps as a result of training In all the patients they were not able to define the fundamental frequency, since noise does not permit the registration of tones

Damste (1958), who included a few sonagrams in his extensive study, states that the average frequency was 67 5 cps, noting that the fundamental tone of an oesophageal voice is often difficult to determine »This is because the frequency is low and because the sound is very complex, in other words the fundamental tone is accompanied by a large number of relatively strong overtones There is in oesophageal speech relatively more energy in the high frequency than in normal speech» Winckel (1958) also drew attention to this fact, as did Luchsinger before him, the latter found that the fundamental tone varied from 50 to 64 cps in tests with a sound frequency spectrometer Van den Berg & Moolenaar-Bijl (1959), reporting their results with the same apparatus, stated that »generally the pitch of oesophageal speech is rather low, between 50—100 cps» According to Curry & Snidecor's (1961) results with the phonophotographic technique, the fundamental frequency of oesophageal speech was 63 3 cps and according to Pantyukhin (1961), using the stroboscope, 60—100 cps

Luchsinger (1952) noted that the fundamental pitch varied from a third to an octave, whereas Curry & Snidecor said that the mean variation of the fundamental tone of laryngectomees was 6 5 tones Tato et al directed interest to variation in fundamental pitch for various vowels, stating that the vowel o is always of higher pitch than the others

The pertinent literature is in full agreement on two points related to post-laryngectomy voice Curry & Snidecor have expressed this as follows » it is obviously very low in pitch, and it is severely limited in the preceived range of pitch variability»

All laryngectomized subjects however, do not acquire the technique of oesophageal speech in spite of having to all appearances similar starting points Those who do not, represent one-third of all laryngectomees as estimated consistently by various experts (Pitkin 1953, McCall 1955, Damsté 1958 Kindler 1960, Svane-Knudsen 1960, Nessel 1963) Artificial larynxes of

various types have been designed to help this group of patients, both mechanical (e g Gluck 1904, Botey 1914, Tapia 1954) and electrically operated devices (e g Briani 1946, Kindler »Pipa de Ticchione» 1953, Pichler 1961) Indeed in the National Hospital for Speech Disorders in New York a special committee has been appointed for this purpose (Advisory Committee on Artificial Larynxes) Levin (1952) gives a list of the indications governing the use of an artificial larynx

(1) *Stenosis of the oesophagus after extension removal of a widespread* malignant lesion; (2) resection of the cervical portion of the oesophagus, (3) multiple handicaps, for example laryngectomy and deafness, (4) suspected recurrence, metastasis, or multiple lesions, for example a bronchial carcinoma in addition to the laryngeal lesion, (5) senility or other feebleness

It seems not to be difficult to learn to use an artificial larynx and make oneself fairly well understood by this means However, the mere fact that this is an artificial device is associated with such undesirable factors as cannot be disregarded Bangs et al (1946) prefer oesophageal speech to the artificial larynx and stress three points (1) it is more natural in quality, (2) there are no appliances which are conspicuous or embarrassing, (3) *the speaker is not dependent upon devices subject to mechanical failure*

Damsté (1958) makes the following three points

(1) *In the electrical type the sound is monotonous*, (2) speech is accompanied by the uninterrupted buzzing sound of the vibrator, (3) when the apparatus is not at hand or out of order, the patient is unable to speak, (4) despite its small size and its many subtle disguises the modern apparatus is still a constant reminder of the patient's disability, both to himself and to his friends (5) the cost of purchase and maintenance is still not negligible

In cases in which oesophageal speech for some reason or other does not succeed the laryngectomized person still has recourse to the so-called parabuccal speech Van Gilse (1949) has stated that an air-bubble is then formed between the cheek and the jaw By muscular action air is forced through a small opening between or behind the teeth into the mouth This gives the basic sound mixture By articulation speech results Such speech, according to Damsté 1958, is of theoretical interest only, and is not recommendable *for rehabilitation purposes*

Laryngectomees who have had no speech training try to make themselves understood for instance at home by using *a kind of forced articulation*, the pseudowhisper Speech of this kind has very little power, yet it can sometimes be fairly well understood, at least by a trained listener, because the greater part of the information consists of sounds of plosive type

What is most important and most difficult in teaching the laryngectomee to speak is to make the required air enter the oesophagus * The classical

* The junction of the hypopharynx and oesophagus usually lies at the level of the sixth cervical vertebra An extension of the pharyngeal *muscles* is the thick layer of striated muscle in the pars cervicalis of the oesophagus The oesophageal orifice is closed by fibres of the m laryngopharyngeus (constrictor pharyngis inf), which are

German method was based on the intake of air at fir[...]
or carbonated drinks But speech thus acquired prove[...]
ed the air mostly went down as far as the stomach [...]
well as the carbon dioxide liberated — bubbled up [...]

Seeman (1961) has stated that speech exercises are [...]
an eructation from the oesophagus, not from the s[...]
prephonatory phase, air can be taken into the [...]
ways (1) by inhalation during the inspiratory pha[...]
by swallowing, (3) by »injection» through articulatory [...]

In Seeman's method, used in several phoniatric c[...]
in Finland, air is propelled direct upward from the [...]
of a »refined eructation» This occurs in such a [...]
head bent slightly forward, the tongue is placed [...]
forcing the tongue upwards towards the palate with [...]
a pressure is produced in the posterior part of the [...]
If the oesophageal sphincter is successfully relaxed a[...]
at this exact moment phonation is attempted using a [...]
combination The most disturbing factors in this [...]
relaxation and simultaneous contraction of the soft [...]
muscles It is frequently of advantage that at the s[...]
of air be insufflated through a thin Nelaton catheter [...]
into the oesophagus Air is then brought up [...]
patient hears his own »voice», can form with [...]
easiest, and so acquires courage and a will to try

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under control of the will but usually act reflexly both [...]
»Active contractions» which in laryngectomized subjects [...]
oesophagus are produced by striated muscles some of which [...]
phragm. The reflex pathway leading to the brain is conne[...]
of the trigeminal nerve and with the pharyngeal branches [...]
the n. laryngicus cranialis The centre of deglutition is loca[...]
close to the vagus nucleus The centrifugal reflex path[...]
nerves which supply the muscles required for swallowing[...]
ramus mylohyoideus of the trigeminal nerve, the glosso[...]
rami of the recurrent nerve in the cervical portion of the [...]
laryngopharyngicus together with the component fibres of [...]

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BASIC PROPERTIES OF SPEECH SOUNDS

The syllabic sounds — vowels — constitute acoustically the basis of all speech. This applies in particular to the Finnish language, where for every 100 vowels, 96 consonants are used, i.e. less than in any of the sixteen languages for which this ratio has been calculated (Hakulinen 1961).

Each vowel[1]) has its own peculiar sound quality based on the distinctive acoustic structure of the vowel concerned. The latter is determined by the so-called formants, which are harmonics or groups of harmonics reinforced in the resonance cavities of the vocal tract. Some of the formants always have fixed frequency positions irrespective of the vowel phonated, whereas others vary in frequency depending upon the vowel concerned. The former, or *fixed formants*, are generated in the cavities which remain almost unchanged in volume, for example the resonance cavities of the thorax, larynx and nose. The latter, or *variable formants*, are generated in the cavities of adjustable volume, such as the pharyngeal, oral and labial cavities (Sovijärvi 1938 a). Since the formant frequencies are not absolutely constant, it seems advisable to use the concept 'formant zone' or 'formant variation area'.

Of the above two groups of formants, the former (fixed formants), have the main function of giving the voice its fundamental pitch and individual resonance characteristics, while the latter (variable formants) make the sounds identifiable as certain phonemes.

From the point of view of acoustic observation there are four important vowel formants. They are termed F 1, F 2, F 3 and F 4, according to their order in the spectral display from low to high frequencies, F_0 denoting the frequency of the voice fundamental.

The lowest two formants are said to be variable, since their positions for the various vowel sounds change appreciably. The fourth and higher formants are referred to as fixed formants, due to their relatively small

[1]) Physiologically the eight Finnish vowels are specified as follows (*Sovijärvi* 1963):

- a = unrounded open back vowel (ask)
- e = unrounded half-close front vowel (head)
- i = unrounded close front vowel (it, eat)
- o = rounded half-close back vowel (*row*)
- u = rounded close back vowel (foot, soon)
- y = rounded close front vowel (does not exist in English)
- ä = unrounded open front vowel (at)
- ö = rounded half-close front vowel (does not exist in English)

variations in speech The third formant has an intermediate position. The relative importance of the separate formants of voiced sounds decreases with increasing order above F 2 F 1 and F 2 are the main determinants of vowel quality F 3 and F 4 contribute significantly to the phonetic quality of front vowels, but in back vowels they are of minor importance only» (Fant 1960) The identification of the back vowels of standard Finnish depends on F 1 and F 2 however, the acoustic distinctness of the front vowels *a* and *o* presupposes the presence of F 3, which in the case of the other front vowels is an absolute requirement (Sovijarvi 1955)

All the lowest three formants are more or less influenced by standing wave resonances (Dunn 1950) Fant (1959) states as follows »F_1 and F_2 are not invariably related to a back and front cavity Those circumstances under which this relation does hold are rather particular involving a clear separation of a medium size front cavity from a back cavity, and further some degree of lip-rounding In back vowels both F_1 and F_2 are substantially dependent on front and back parts of the vocal tract The same is true of F_2 and F_3 of front vowels F_1 of front vowels is dependent on the vocal tract and pharynx acting as a capacitance and the whole of the mouth as an inductance When the tongue is in the i-position, there will be a clear dependency of F_2 on a standing wave resonance effect in the back cavity, i e in the pharynx F_3 is then mainly influenced by the mouth cavity. The back cavities have a greater influence on F_1 of *u*, *o* and *i*, while the cavity system in front of the tongue constriction has an appreciable effect on *a* and *e* »

Sovijarvi (Ylppo and Sovijarvi 1962) says that the areas where these formants are generated in the dentals analysed by him are as *follows*

»F 1 = pharyngeal formant, depending mostly on the pharyngeal cavity (situated behind the tongue channel)

F 2 = oral formant, depending mostly on the oral cavity (situated in front of the tongue channel)

FS = subdorsal or preoral formant (The channel between the *incisors* forms the front aperture of the subdorsal cavity, the back aperture being formed by the channel below the alveolar arch which, however, is either completely or nearly closed in dental consonants) This formant corresponds to the third formant »F 3» in the vowel spectra

F 4 = formant of the vestibule of the larynx »

Only when the first two formants are well separated is it possible to say that the first depends more upon one cavity, the second upon another (Dunn)

By combining the three types of vocalization, speech, singing and whisper, the maximum variation areas of the formants in the case of each vowel can be determined These variation areas for the main variable formants, F 1 and F 2 have been determined by Sovijarvi (1938 b) by using seeker-tone analysis, sound frequency spectrometer and Fourier analysis. His results are presented in Table 1

TABLE 1 *Sovijärvi's (1938 b) measurements of the maximum variation areas of F1 and F2 presented in three groups according to the position of F1 (a-ä, o-ö-e and u-y-i)*

	F1			F2		
a	630—890	cps	(dis^2—a^2)	960—1130	cps	(h^2—d^3)
ä	630—860	»	(dis^2—a^2)	1345—1900	»	(f^3—h^3)
o	450—645	»	(a^1—e^2)	640—895	»	(e^2—a^2)
ö	405—540	»	(gis^1—c^2)	1520—1730	»	(g^3—a^3)
e	255—510	»	(c^1—h^1)	1600—2340	»	(ais^3—cis^4)
u	360—450	»	(fis^1—a^1)	600—645	»	(d^2—e^2)
y	255—425	»	(c^1—a^1)	1665—1800	»	(gis^3—ais^3)
i	255—450	»	(c^1—a^1)	2240—2550	»	(cis^4—e^4)

Wiik (1961) has later determined the variation areas of the formants of Finnish sustained vowels by using sounds synthesized by the speech sytnhesizer Ove 2, constructed by Fant. In the sounds F1 varies from 200 cps up to 900 cps and F2 from 600 cps up to 2600 cps. F3 and F4, as well as F_0 values, were fixed at 2800 cps, 3280 cps, and 120 cps respectively. (F_0 rises towards the end of the sounds.) All the Finnish vowels can be defined using the following boundaries:

a	$F_1 > 570$ cps and		$F_2 - F_1 < 600$ cps
ä	$F_1 > 570$ » »		$F_2 - F_1 > 600$ »
o	380 cps $< F_1 < 570$ » »		$F_2 - F_1 < 600$ »
ö	350 » $< F_1 < 570$ » »	$F_2 - F_1 > 600$ cps and	$F_2 + F_1 < 2400$ »
e	350 » $< F_1 < 570$ » »		$F_2 + F_1 > 2400$ »
u	$F_1 < 380$ » »		$F_2 - F_1 < 550$ »
y	$F_1 < 350$ » »	2100 cps <	$F_2 - F_1 < 2400$ »
i	$F_1 < 350$ » »		$F_2 + F_1 > 2400$ »

Wiik's results are found to be roughly consistent with those of Sovijärvi.

Females have, on the average, one octave higher fundamental pitch and 17 per cent higher formant frequencies (Peterson and Barney 1952, Fant 1953). The frequency of the formant is affected, as is well known, by the volume of the cavity where it is generated, in such a manner that the formant frequency rises with a decrease in cavity volume.

Being vowel sounds which change in acoustic quality with changes in the position of the tongue and lips, there occurs in the diphthongs a formant glide such as is required by the situation at any one time. Each of the diphthongs produces a distinctive pattern consisting of the initial vowel position from which the glide starts, the glide, and the second vowel position where the glide terminates (Potter et al. 1947). Finnish vowel harmony requires that a word contains either only front vowels or only back vowels, so that no vowel combinations requiring a remarkably great glide can occur. The front vowels e and i, however, can occur in combination with back vowels too, and it is exactly in these cases that the most marked formant glides are noted.

Although formants are characteristic of vowels, they play an important part in the acoustic identifiability of certain consonants According to Sovijarvi (1961), the consonants of standard Finnish may be classified on the basis of sound components as follows formant consonants (nasals, laterals and semivowels), noise consonants (unvoiced spirants, sibilants and plosives), and noise-formant consonants (tremulants and voiced plosives)

A thorough investigation into the sound components of the Finnish consonants has not yet been made, but there are Palva's (1958 a and b) spectrographic studies of the structure of Finnish consonants and vowels, both spoken and whispered, as well as Sovijarvi's (1938 b, -59, 61, -62) results of measurements, obtained chiefly by seeker-tone analysis and sonagraphically

In the consonants the energy concentrations, the formants or components, are as follows

Semivowels	*v*	200—500 cps	1400—8000 cps
	j	250—500 »	2100—6800 »
	h	has relatively weak intensity because it is generated in the half-open glottis Its formants have the same positions as the adjacent sounds	

The glide of F 2 is to be considered a special characteristic of the semivowels (Potter et al) However, the voiced *h*, in which this glide is more limited, is a case apart.

Liquids	*l* lateral	400—1200 cps	1700—3200 cps
	r tremulant	250—1800 »	2050—4850 »

Nasals *m*, *n* and *ŋ* The formants typical of all nasals are

FN 1 = formant of the epi hypopharyngeal cavity	200— 250 cps
FN 2 = formant of the epi pharyngeal cavity	1300—1600 cps

Formants of the lower (inferior), middle (medius) and upper (superior) nasal passage, respectively

FN 3 inf	1950—2300 cps
FN 3 med	2300—2700 »
FN 3 sup	2700—3300 »
F 4	3300—3450 »

The vowel formants proper are of secondary importance in the nasals F 1 is found to be 300—430 cps, F 2 500—1900 cps, and F 3 1800—2600 cps The nasal *m* lacks a third formant because of the bi labiality of this sound

Fant (1960) has stated »The effect of the mouth cavity as a side chamber, shunting the sound transmission through the pharynx-nose system is to cause a shift of resonance frequencies and to introduce anti-resonances It has been verified by supplementary analog experiments that an increase of the coupling area to the mouth cavity, as in

TABLE 1 *Sovijärvi's (1938 b) measurements of the maximum variation areas of F1 and F2 presented in three groups according to the position of F1 (a-d, o-o-e and u-y-i)*

	F1			F2		
a	630—890	cps	(dis—a)	960—1130	cps	(h—d^1)
a	630—860	»	(dis—a^2)	1345—1900	»	(f^1—h^1)
o	450—645	»	(a^1—e^2)	640—895	»	(e^2—a^2)
o	405—540	»	(gis^1—c^2)	1520—1730	»	(g^3—a^3)
e	255—510	»	(c^1—h^1)	1600—2340	»	(ais^3—cis^4)
u	360—450	»	(fis^1—a^1)	600—645	»	(d^2—e^2)
y	255—425	»	(c^1—a^1)	1665—1800	»	(gis^3—ais^3)
i	255—450	»	(c^1—a^1)	2240—2550	»	(cis^4—e^4)

Wiik (1961) has later determined the variation areas of the formants of Finnish sustained vowels by using sounds synthesized by the speech sytnhesizer Ove 2, constructed by Fant In the sounds F1 varies from 200 cps up to 900 cps and F2 from 600 cps up to 2600 cps F3 and F4, as well as F_0 values, were fixed at 2800 cps, 3280 cps, and 120 cps respectively (F_0 rises towards the end of the sounds) All the Finnish vowels can be defined using the following boundaries

a	$F_1 > 570$ cps and		$F_2 - F_1 < 600$ cps
a	$F_1 > 570$ » »		$F_2 - F_1 > 600$ »
o	380 cps $< F_1 < 570$ » »		$F_2 - F_1 < 600$ »
o	350 » $< F_1 < 570$ » »	$F_2 - F_1 > 600$ cps and	$F_2 + F_1 < 2400$ »
e	350 » $< F_1 < 570$ » »		$F_2 + F_1 > 2400$ »
u	$F_1 < 380$ » »		$F_2 - F_1 < 550$ »
y	$F_1 < 350$ » »	2100 cps <	$F_2 - F_1 < 2400$ »
i	$F_1 < 350$ » »		$F_2 + F_1 > 2400$ »

Wiik's results are found to be roughly consistent with those of Sovijärvi

Females have, on the average, one octave higher fundamental pitch and 17 per cent higher formant frequencies (Peterson and Barney 1952, Fant 1953) The frequency of the formant is affected, as is well known, by the volume of the cavity where it is generated, in such a manner that the formant frequency rises with a decrease in cavity volume

Being vowel sounds, which change in acoustic quality with changes in the position of the tongue and lips, there occurs in the diphthongs a formant glide such as is required by the situation at any one time Each of the diphthongs produces a distinctive pattern consisting of the initial vowel position from which the glide starts, the glide, and the second vowel position where the glide terminates (Potter et al 1947) Finnish vowel harmony requires that a word contains either only front vowels or only back vowels, so that no vowel combinations requiring a remarkably great glide can occur The front vowels e and i, however, can occur in combination with back vowels too, and it is exactly in these cases that the most marked formant glides are noted

MATERIAL AND METHODS

1. Material

The case material under discussion consists of the voice samples of 27 *oesophageal speakers* laryngectomized for carcinoma of the larynx in the period 1953—1962 All the test subjects were men, 14 had been operated at the Oto-laryngological Clinic of the University of Turku, 11 at the Oto-laryngological Clinic of the University of Helsinki, and 2 in the Third Medical Department (Kivela Hospital) in Helsinki

The series, representing both town and country population and different educational standards, was selected so as to consist of only good oesophageal speakers in whom, on the basis of periodical acoustic observations sometimes covering many years, oesophageal voice development could be considered terminated All those accepted into the series had normal hearing

To exclude any speech other than the oesophageal, all the patients were subjected to indirect pharyngoscopy and 14 in addition to a simultaneous stroboscopy with these procedures it was checked that the produced oesophageal voice caused vibrations at the orifice of the oesophagus

The cases, numbered in alphabetical order 1—27, averaged 51 years and 4 months in age, the age distribution is shown in table 2 The table also indicates the number of laryngectomized subjects on whom unilateral neck dissection was performed and of those who received postoperative roentgen therapy Four patients had been given roentgen ray therapy before operation.

TABLE 2 *Material*

Age at time of laryngectomy	Number of cases	Neck dissection	Rtg treatment
31—40	4	1	3
41—50	8	3	7
51—60	12	6	11
61—70	3	—	2
Total	27	10	23

All the laryngectomized patients were given phoniatric treatment as soon as their postoperative status permitted it, the aim being to teach them the technique of oesophageal speech by the air injection method previously described. Training varied in the different cases from a few sessions up to about 50 The patients themselves were of the opinion that they acquired

the ability to use the oesophageal voice sooner or later but they could not fix the time when they did so Evidently this occurred from two weeks to six months after operation

The patients admitted to the series had been using the oesophageal voice for the following periods of time

½— 1 year	5 subjects
1— 2 years	4 »
2— 3 »	2 »
3— 4 »	2 »
4— 5 »	7 »
5— 6 »	2 »
6— 7 »	— »
7— 8 »	3 »
8— 9 »	1 subject
9—10 »	1 »
	Total 27 subjects

Six oesophageal speakers (Nos 2, 10, 11, 12, 15, 25) were selected arbitrarily for cineradiographic examination

To obtain a suitable control series, 25 men equalling the laryngectomees in age were selected, having voices of a quality well corresponding to the loss of laryngeal tones in the laryngectomees Hence it may be assumed that the results in the control cases are well comparable with those to be reported below for oesophageal speakers

2. Apparatus

A Sound spectrography

The sound spectrograph »Sona-Graph» (manufactured by the Kay Electric Company, Pine Brook, N Y) was used for the analysis of the physical quality of oesophageal speech The Sonagraph has been described in greater technical detail by Potter et al and Prestigiacomo (1957)

With this apparatus it is possible to analyse 2 4 secs of material, the extent of frequency variation being 80—8000 cps The voice sample is recorded on the magnetic drum of a rotating disk It can be reproduced in continuous repetition on to nonphotographic, electrically sensitive, and facsimile-type paper The paper is wrapped round a drum rotating in synchronism with the above-mentioned disk Thus, time is shown along the horizontal axis and frequency along the vertical axis There is a choice of two analysing filters, a narrow (band-width 45 cps) and a wide one (300 cps), the former is better because it allows more accurate measurements of the formant positions in frequency amplitude sections It was used in all the tests to be described below

In the sonagram thus obtained, various details can be elucidated by means of section, or instantaneous voice spectrum (30 msec), along the time axis of the sonagram The section, having a maximal amplitude of 35 dB, increases along the horizontal axis from left to right, the frequency increasing along the vertical axis downwards Section is particularly well adapted for analysis of formant structure and intensity of individual sounds When studying the coupling and intensity variations of words and sounds it is possible to use an amplitude curve with an intensity scale up to 24 dB The curve is recorded above the original sonagram and it can be lowered by 10 dB, so that the sound limits can be more clearly identified in the presence of two intensity curves Possible adjustment of the zero line can also be utilized to advantage in this respect

B Cineradiography

To determine the site and shape of the pseudoglottis, a cineradiogram was made with a 5' Philips image intensifier with accompanying 35 mm. Arriflex film camera The tube used was a »Muller-Öl-Rotalix Rohre» 30 kW with 0 3 x 0 3 mm. focus Total filtration 2 mm. Al The exposure data were 70 kV at 4—5 mA The film was Gevapan 36 All exposures were made at the speed of 20 frames/sec, the roentgen focus being directed to the hypopharynx

The developed film was analysed in a Philips viewer in which the film is projected on to a translucent screen In this viewer the film can be projected frame by frame or continuously at any desired speed up to 24 frames/sec The film can be run both forwards and backwards in this projector An automatic counter makes it possible to find each particular frame of the cinefilm.

3 Methods of the investigation

To bring out each of the phonetic factors of Finnish speech the test subjects were asked to say all eight vowels separately and in addition the 63 test words of the vocabulary list in Table 3 These latter had been chosen in such a way that the three most important vowels, two back vowels the open unrounded *a* and the close rounded *u*, as well as the close unrounded front vowel *i*, occurred on each side of all single and double consonants Thus it was possible to make observations concerning the consonant variants having the colour of *a*, *u* and *i* When the test words permitted it, attention was paid also to the acoustic pattern of initial consonants. The 16 diphthongs occurring in Finnish speech, 13 narrowing and 3 opening ones, as well as the vowel combinations *iy* and *ey* to



Fig 1 Sound reproduction curves of microphone (— — —) and tape recorder (———) in the frequency range of the Sonagraph 80—8000 cps

be included among the diphthongs, were also analysed and are presented in Table 3 Four additional consonants occurring in younger loan words (b, g, š, f) were disregarded in this connection

All recordings were made in the camera silenta of either the Department of Physiology, University of Turku, or the Otolaryngological University Clinic, Helsinki, using the high-quality, dynamic »Uher Breitband-Mikrofon Typ 621» with sound reproduction range of 40—16,000 cps (almost linear reproduction up to 3000 cps) (Fig 1), and a sensitivity of 0 18 mV/Mikrobar The speech was directed perpendicularly to the microphone from a distance of about 30 cm and recorded with a Grundig TK 24 tape recorder with the maximal fluctuation of ± 0 2 %, range of reproduction 40—14,000 cps (most linear reproduction in the area 200—2000 cps) (Fig 1) Reproduction pitch was checked with a control lamp, using as accessory equipment an in-built microphone front amplifier on the output side of the tape recorder, this tube could be connected directly with the Sonagraph for analysis of the recordings

The results were further analysed by presenting recorded samples to an auditory observation group — on an average five persons — who, independently of one another, noted down their observations on paper Thus the distinctness of the voices concerned could be established

The test subjects studied by cineradiography[1]) pronounced the most important vowels (*a, u, i*) included in the vocabulary list both with and without opaque medium ($BaSO_4$)

4. Statistical methods

The fundamental frequencies of the different vowels to be dealt with later in this study were compared mathematically using the so-called »null hypothesis», based on the assumption that the fundamental frequencies concerned are representative of the same normally distributed material The null hypothesis may be considred disproved only if $s_2^2 > s_1^2$, where s_2^2 is the dispersion of mean frequency values for the different vowels and s_1^2 is the dispersion of individual frequencies

[1]) These tests were performed at the Cardiorespiratory Research Unit of the Department of Physiology Turku University

TABLE 3 *Finnish test material The stress is always the first syllable A colon (:) is put after long vowels and double consonants*

Vowels	a (*a*), e (*e*), i (*i*), o (*o*), u (*u*), y (*y*), ä (*ä*), ö (*ö*)					
Diphtongs	kaikki	(*kaik:i*)	kuikka	(*kuik:a*)	eukko	(*euk:o*)
	keikkua	(*keik:ua*)	kyökki	(*kyök:i*)	loiko	(*löikö*)
	kiekko	(*kiek:o*)	koykkia	(*köyk:iä*)	kyikky	(*kyik:y*)
	koukku	(*kouk:u*)	kaukaa	(*kauka:*)	täyttaa	(*täyt:a:*)
	kuokka	(*kuok:a*)	koikka	(*koik:a*)	vilhytyä	(*vil:ytyä*)
	kiukku	(*kiuk:u*)	taiko	(*täikö*)	keskeytya	(*keskeytyä*)
Vowel-like sounds	raaja	(*ra:ja*)	aava	(*a:va*)	maahan	(*ma:han*)
	piiju	(*pi:ju*)	liivi	(*li:vi*)	piihin	(*pi:hin*)
	kuuju	(*ku:ju*)	puvun	(*puvun*)	kuuhun	(*ku:hun*)
Liquids	jaala	(*ja:la*)	tallat	(*tal:at*)		
	siili	(*si:li*)	pillit	(*pil:it*)		
	kuulu	(*ku:lu*)	tullut	(*tul:ut*)		
	vaara	(*va:ra*)	parrat	(*par:at*)		
	viiri	(*vi:ri*)	mirrit	(*mir:it*)		
	huuru	(*hu:ru*)	purrut	(*pur:ut*)		
Nasal sounds	naama	(*na:ma*)	mamma	(*mam:a*)		
	riimi	(*ri:mi*)	mimmi	(*mim:i*)		
	luumu	(*lu:mu*)	mummu	(*mum:u*)		
	jaana	(*ja:na*)	nannat	(*nan:at*)		
	viini	(*vi:ni*)	pinnit	(*pin:it*)		
	ruunu	(*ru:nu*)	hunnut	(*hun:ut*)		
	langan	(*laŋ:an*)				
	tingin	(*tiŋ:in*)				
	rungon	(*ruŋ:on*)				
Fricative sounds	haapa	(*ha:pa*)				
	hiipi	(*hi:pi*)				
	hunnut	(*hun:ut*)				
	raasa	(*ra:sa*)	massa	(*mas:a*)		
	riisi	(*ri:si*)	hissi	(*his:i*)		
	ruusu	(*ru:su*)	sussu	(*sus:u*)		
Plosives	haapa	(*ha:pa*)	pappa	(*pap:a*)		
	hiipi	(*hi:pi*)	vippi	(*vip:i*)		
	uupua	(*u:pua*)	huppu	(*hup:u*)		
	naakat	(*na:kat*)	takka	(*tak:a*)		
	piikit	(*pi:kit*)	tikki	(*tik:i*)		
	luukut	(*lu:kut*)	tukku	(*tuk:u*)		
	maata	(*ma:ta*)	matta	(*mat:a*)		
	liitin	(*li:tin*)	kitti	(*kit:i*)		
	muutu	(*mu:tu*)	tuttu	(*tut:u*)		
	kaadan	(*ka:dan*)				
	liidin	(*li:din*)				
	puudun	(*pu:dun*)				

$$s_2^2 = \left[\sum_1^n (\sum_1^{N_i} x_i)^2/N_i - (\sum_1^N x)^2/N \right] /(n-1)$$

$$s_1^2 = \left[\sum_1^N x^2 - \sum_1^n (\sum_1^{N_i} x_i)^2/N_i \right] /(N-n)$$

where n = the number of vowels (8)
N_i = the number of subjects (18)
N = n · N_i (= 144)
x = the individual frequency value
x_i = the individual frequency value of separate vowel

The so-called Wilcoxon test, illustrated below by means of two random samples of a continuous distribution of unknown form, was used to demonstrate statistically significant differences between mean frequencies of vowel formants

The number of control subjects $N_1 = 25$ and that of the test subjects $N_2 = 27$ The test subjects and the controls are arranged, in the case of each vowel formant, in order according to frequency level, starting from the lowest frequency, each subject being given a running number. 1, 2, 3 51, 52 ($25 + 27 = 52$) In case several persons fall under one and the same frequency value, the running number given each of them is the mean running number for the group concerned

Example F 1 of *a*

Frequency	560	600	640	680	720	760	780	800	880
Number of test subjects	1	1	2	1	7	1	1	8	5
Number of control subjects	6	1	9	4	5	—	—	—	—
Running number	4	8.5	15	23	31	38	39	43.5	50

The sum T_1 of the running numbers obtained for the control subjects is calculated In accordance with the null hypothesis the waiting value for T_1, T_1, is

$$N_1 (N_1 + N_2 + 1)/2 = 662.5 \text{ cps}$$

$$\text{Variance } \sigma^2_{T_1} = N_2 T_1/12$$

The probability of error being $P = 0.05$ the control group frequencies are to be considered to represent a lower frequency level than the corresponding frequencies in the test group when $T_1 = 571$ cps (according to a table in Documenta Geigy, Wissenschaftliche Tabellen 6th edition 1960, p 128)

CHAPTER V

SOUND SPECTROGRAPHIC RESULTS

1. Fundamental pitch

There is a question which should perhaps be considered before dealing mith the voice quality of oesophageal speakers *What is the fundamental* pitch of the oesophageal voice? This is frequently difficult for the human ear to detect, and the difficulty is due to a combination of factors

The most important of these is the low frequency of the fundamental tone and the fact that the fundamental and its over-tones are accompanied by additional noise, the breath sound — a murmur or gurgling noise — from the tracheostoma is very prominent. The vibrations of the pseudoglottis may be aperiodic, in which case only noise and no periodic sound results The volume of air in the oesophagus varies and this causes changes in subglottic pressure Accumulation of mucus in the hypopharynx gives rise to considerable difficulties in many cases The air utilized in speaking then has to be forced through layers of secretions of variable thickness, and the result is a noise rather than a resonant tone

For the above reasons it is not always possible to determine in oesophageal speakers the vibration of the fundamental tone or subglottis, viz. the frequency To a reliable degree, vowel by vowel, this was only possible in 18 oesophageal speakers The measurements were made at the middle of each vowel, they are presented in Table 4

Vibration of the fundamental was found to vary in single vowel samples from 32—72 cps and the means for the individual test subjects from 36 7—60 5 cps, giving the average 50 4 cps for the laryngectomees In the control group the corresponding mean was 104 0 cps In Fig 2 these mean fundamental frequencies are shown in a musical scale (F-clef), which indicates graphically that the mean frequency level of an oesophageal speaker is nearly a full octave below that of a normal speaker

It is well nigh impossible for laryngectomees to produce at will a change in the fundamental tone in one direction or another Unconsciously this has

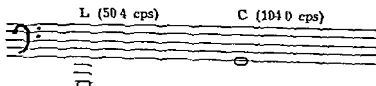


Fig 2 Mean values for vibrations of fundamentals in laryngectomized (L) and control group (C) presented in a musical scale

TABLE 4 *Frequency of fundamental tone in 18 oesophageal speakers in whom such recording was possible vowel by vowel The recording was made from the middle of each vowel*

Subjects Number	Vowels a	e	ı	o	u	y	ä	o	Mean Frequency of Subject
18	64	64	60	60	72	52	56	56	60.5 cps
20	56	64	56	52	56	56	56	52	56 0 »
11	52	48	48	56	60	60	64	60	56 0 »
1	52	48	64	64	56	64	52	48	56 0 »
19	48	68	56	48	56	60	56	44	54 5 »
8	52	52	52	56	56	52	60	56	54.5 »
5	52	52	52	48	60	60	48	56	53.5 »
15	56	52	52	52	48	60	52	56	53.5 »
25	56	52	60	52	48	48	56	56	53.5 »
12	56	56	40	52	40	64	44	60	51.5 »
10	56	44	36	68	48	52	48	36	48.5 »
23	52	44	48	48	44	44	52	48	47.5 »
26	52	48	44	44	40	40	48	56	46.5 »
9	48	36	48	48	48	48	44	44	45.5 »
4	52	40	48	56	44	44	36	40	45 0 »
13	52	40	48	44	48	44	40	40	45 0 »
24	52	44	48	40	40	40	36	40	42.5 »
17	36	40	32	32	36	40	40	38	36 7 »
Mean Frequency of Vowels	52 4	49.5	49.5	51.1	50 0	51.5	49.3	49.8	»
Mean Frequency of Group									50 4 »

occurred so the average variation in certain different patients was 14 7 cps, which corresponds to 3—4 tones This was entirely independent of the fundamental frequency and of the vowel being tested The corresponding range of variation in the control group was only 2 5 tones

The average vibration of the fundamental of different vowels was found to differ very little However, all the back vowels reached somewhat higher averages than the front vowels Of these latter, only *y* attained the same level as the back vowels When the back vowels are grouped according to frequency from the lowest to the highest, the order will be *u*, *o*, *a*, which is in exact agreement with the ascending order of the pharyngeal and mouth formants of the back vowels The statistic calculations show that $s_2^2 < s_1^2$ and therefore we may conclude that the quality of the vowels do not have influence on the fundamental frequency It is evident that, because of the altered anatomical conditions, the fundamental frequency of the back vowels as pronounced by the laryngectomees bears a correlation to both F 1 and F 2 Thus the most posterior vowel, *a*, requiring the smallest distance from base of tongue to pharyngeal wall and also arising in closest proximity to the considerably narrowed hypopharynx, evidently retards the expulsion of oesophageal air, thus reinforcing subglottic vibration The other back

determine special stress areas for this noise and even to localize it. Only some shadowing fairly evenly mixed with the subglottic vibrations is noted, and it can extend, apparently evenly, from the lower to the upper end of the sonagram, it seems even beyond the latter (Fig. 2).

Naturally, the disadvantage arising from the tracheostoma noise is directly proportional first of all to the intensity of this noise and also secondly to the extent and location of its frequency range. The intensity of the noise, however, was never found to be of the same order of magnitude as the formants, which generally are shown as dark horizontal bars, but it may make the formants less perceptible especially to acoustic observation — a fact that is of primary importance in the identification of vowels and certain consonants also.

The noise from the tracheostoma is accidental. Indeed the question is here mainly of whether the laryngectomee expires air during speaking and whether this is done with sufficient power for the breath sound to be recognized. It is evident that most oesophageal speakers during speaking hold their breath, at least to some extent, in order to make their voice louder, through increased intrathoracal pressure. In this they succeed. If, however, the subglottis has weak activity with low frequencies, attempts are made to raise this pressure by powerful inspiration to increase the frequency, and this — in the absence of the rima glottidis — also results in powerful expulsion of air and an undesirable noise from the tracheostoma.

TABLE 5 *Mean frequencies of formants F 1, F 2 and F 3 for vowels (cps)*

	F 1			F 2			F 3		
Vowels	oesoph speech		control speech	oesoph speech		control speech	oesoph. speech		control speech
u	358		350	720	*	630	2550		2446
o	504		500	904	*	820	2644		2546
a	765	*	636	1194	*	1140	2632		2570
a	700	*	648	1797	*	1650	2564		2560
e	435		424	2224	*	1950	2918	*	2440
i	332	*	244	2520	*	2172	3380	*	2880
y	295	*	276	1798	*	1720	2563	*	2296
o	478	*	440	1826	*	1540	2515	*	2392

* = difference statistically significant

TABLE 6 *The control mean frequency values for the first three formants of the different vowels given in Table 5 must be regarded as representing a lower frequency group and the difference thus as a statistically significant one, when the probability of error P = 0.05 has the waiting value T_1 in accordance with null hypothesis: this value is underlined in the table for each particular vowel and formant.*

Vowels	u	o	a	a	e	i	y	o	
F1	570.0	641.5	*414.0*	*555.0*	686.5	*402.5*	598.0	*427.5*	cps
F2	*444.0*	*485.5*	*556.5*	*514.0*	*444.5*	*382.5*	*562.0*	*372.0*	"
F3	629.5	571.5	665.5	632.5	*372.0*	*401.5*	482.5	536.6	"

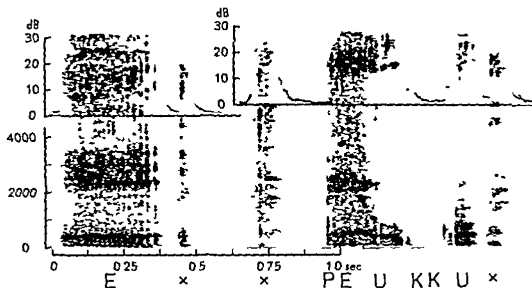


Fig 4 Spectrographic analysis of the sound produced by »air-injection» (×) into the oesophagus This sound usually occurs immediately after phonation when the oesophagus has been emptied of air (E), or both before and after phonation (PEUKKU)

at the onset, may occur, though more rarely, even in the same individual This is because there may be accumulation of mucus, which often makes it difficult to start the voice When the passage has been cleared, the rate of subglotic vibrations increases (Fig 3 ₄)

Occasionally a vowel, even a short one, more rarely a word, is split up into two parts Vibration of the pseudoglottis ceases for over a tenth of a second, which is well perceived by the ear, and then continues for a while mostly at a slower rate than before Oesophageal contractions during this time force the last portions of air into the hypopharynx (Fig $3_{,3}$)

In a few cases a subject had adopted a kind of adjuvant enunciation in order to produce the sound desired This may consist for instance in opening and closing the lips a few times in succession or »tuning» the oesophageal voice by a few successive sounds, or utilizing accessory vowels to make the desired sound item, as at times in dysphemia

In addition to these, the sound caused by air intake into the oesophagus is also heard This swallowing noise is very strong in some cases and thus is also rather disturbing It does not actually interfere with speech when it follows immediately after phonation (Fig 4, E) or occurs both before and directly after phonation (Fig 4, PEUKKU) The sound-energy in the swallowing noise is fairly evenly distributed over the whole frequency scale of the sonagram The intensity is considerable, only about 5 dB less than at the preceding or succeeding sound or word

Extremely undesirable is the occasional noise from the tracheostoma, which may begin during preparation for phonation and continue during and after phonation in the form of a very loud murmur It is impossible to

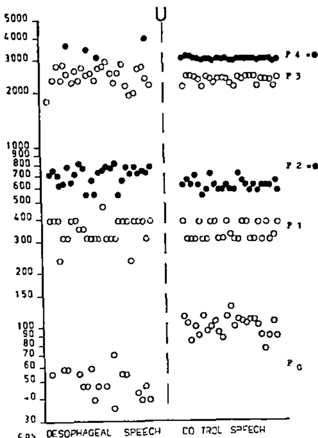


Fig 6 Frequency of F_0 and formants F 1, F 2 F 3 and F 4 for the vowel *u* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

a the only unrounded back vowel, which differed from other back vowels in that its F 1, 765 cps, exceeded considerably the control mean 636 cps Difference statistically significant

The individual F1 values with the corresponding control values will be found in the following figures *u* Fig 6, *o* Fig 7 and *a* Fig 8

Formant 2

In the case of all three back vowels the mouth formant was higher than the corresponding control mean, and this difference was statistically significant The greatest difference was obtained for *u* the mean for the laryngectomees was as high as 720 cps as against 630 cps for the controls

For the vowel *o* the mean frequency of F 2 was 904 cps, and the control value 820 cps

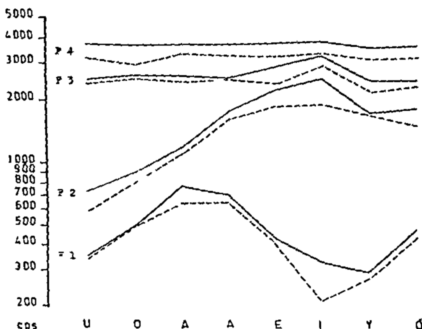


Fig 5 Sequential diagram of oesophageal (——) and control (— — —) speech vowel formants F 1, F 2, F 3, and F 4

2. Formant analysis of Finnish vowels

Another object in analysing the sound quality of oesophageal speech is to determine whether, and if so, to what extent, its vowel formant structure differs from that of standard speech.

The results for the means of the formants F 1, F 2 and F 3 are presented in Table 5, the statistically significant values are shown in Table 6 and diagrammatically in figure 5 on a semilogarithmic scale, also showing the mean formants for the control group Furthermore each vowel is presented in a separate table, where are indicated the values for the different formants in each laryngectomized subject, and side by side with these, the corresponding control results

A Back vowels u, o, a

Formant 1

The back vowels are grouped in order from lowest to highest according to their ascending pharyngeal and mouth formants, F 1 and F 2

u mean F 1 was 358 cps and the corresponding control value 350 cps, difference not statistically significant

o mean F 1 slightly above control mean the former 504 cps, the latter 500 cps, difference not statistically significant

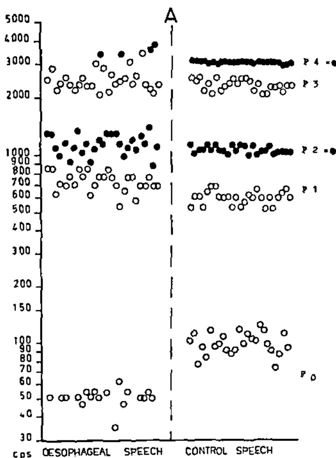


Fig 8 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel *a* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

Formant 4

As the fourth formant was only demonstrated in an occasional case, it will be dealt with in its entirety in connection with the front vowels

B. Front vowels a, e, i, y, o

Formant 1

The front vowels have been dealt with mainly in the order of the ascending mouth formants, the unrounded vowels coming first and and the rounded vowels, representing the medium range of this formant, last

All the front vowels of the laryngectomees had the same common characteristic as the back vowels in regard to F 1 this formant was higher throughout than were the control values Apart from the vowel *e*, the difference

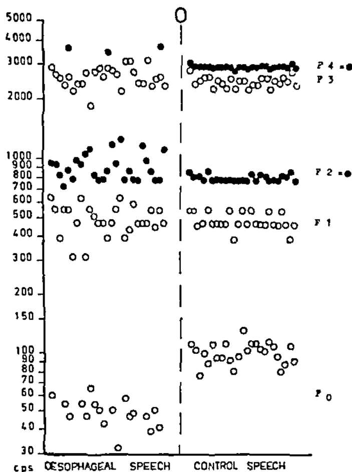


Fig 7 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel *o* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

For *a* the mean frequency of F 2 was 1194 cps, the control value being 1140 cps Thus, here F 2 only increased about one half compared with F 1

The individual values for F 2 are seen in figures 6, 7 and 8

Formant 3

The third formant of the back vowels is of secondary importance from the point of view of acoustic observation It was often very weak, but nevertheless its frequency values were higher than those obtained for the controls and the difference was not statistically significant *u* 2550 cps, controls 2446, *o* 2644 cps, controls 2546 cps, and *a* 2632 cps, controls 2520 cps

The individual values for F 3 appear in figures 6, 7 and 8

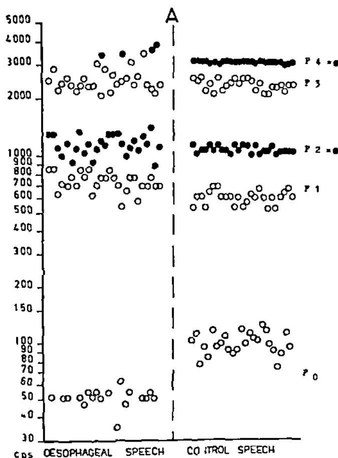


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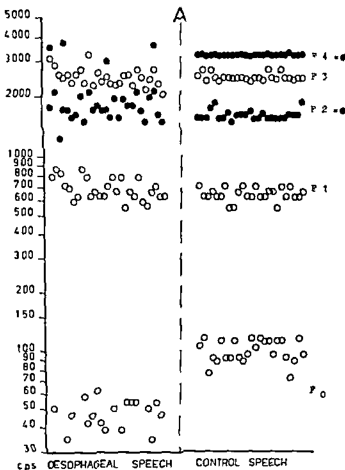


Fig 9 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel *a* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

was statistically significant The difference was most marked in *i* being a close vowel, *i* reached the mean frequency 332 cps This is 88 cps higher than the control value The next greatest difference was obtained in the case of *a* the mean frequency was 700 cps, and the control value 52 cps lower For the vowels next in order in this respect, the difference decreased as follows *o* 478 cps, control value 440 cps, *y* 295 cps, control value 276 cps, and finally *e* with 435 cps and 424 cps respectively

The individual F 1 values for the front vowels and their control values appear in the following figures *a* Fig 9, *e* Fig 10, *i* Fig 11, *y* Fig 12, and *o* Fig 13

Formant 2

Similarly as F 1, F 2 showed higher frequency values in the laryngectomized subjects than in the controls the differences were also statistically significant

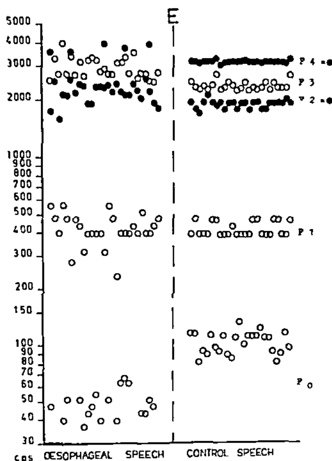


Fig 10 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel *e* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

Studying the differences in order from largest to smallest, the order was found to be the same as for F 1, but *e* occupied the place of *a*, and thus came second Thus *i* shows the highest frequency of mean F 2, 2520 cps, and the control value 2172 cps, the difference 348 cps is remarkably great The results for the next vowel *e* are respectively 2224 cps and 1950 cps, for *o* 1826 cps and 1540 cps, for *a* 1797 cps and 1650 cps, and for *y* 1798 cps and 1720 cps

The individual F 2 values are given in figures 9, 10, 11, 12 and 13

Formant 3

The third formant resembles the first and second in that the frequencies tend to be higher than the control values, *a* being the only vowel to display no statistically significant difference If these differences are compared, it is seen that the maximum difference, 500 cps, appeared in the case of *i*, mean

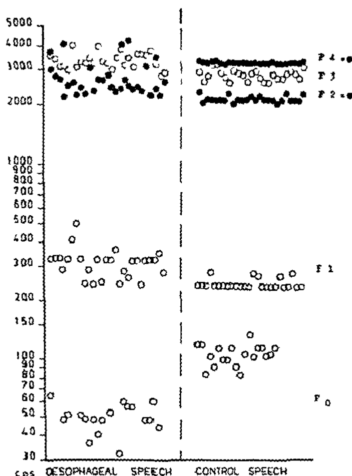


Fig 11 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel *i* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

frequency 3380 cps The highest frequency value was obtained here, as in the case of the preceding formant, for the vowel *i*, the corresponding control result being 2880 cps. The difference for *e*, is 478 cps. It will be seen that in *i* and *e* the difference between the laryngectomized and the control persons is almost identical Third in the series was *y* with the figures 2568 cps and 2296 respectively, and next came *o* with 2515 and 2392 cps The frequency value for *a* was only 4 cps higher than the control value, 2564 cps and 2560 cps respectively

The individual frequencies of F 2 are found in figures 9, 10, 11, 12 and 13

Formant 4

In 15 laryngectomized subjects the fourth formant could be identified for none of the vowels, and in none of the subjects for all of the vowels In only one laryngectomee was F 4 identifiable in six vowels, in 2 subjects in five

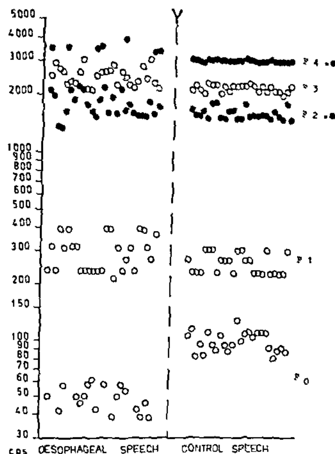


Fig 12 Frequency of F_0 and formants F1 F2 F3 and F4 for the vowel *y* The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

vowels there were also 2 subjects with F4 demonstrable in four vowels 1 subject with F4 in three vowels, and six with F4 in only two vowels In this way, however, it was possible to determine some kind of mean F4 for each of the vowels, this mean and the number of formants recognizable in each case are listed below together with the respective control values

Vowels		Oesophageal speech		Control speech
u	F4	3760 cps/4 (number of formants)		3200 cps
o	F4	3720 • /3	•	3050 •
a	F4	3760 • /4	•	3380 •
a	F4	3720 • /4	•	3350 •
e	F4	3800 • /5	•	3300 •
i	F4	38_0 • /5	•	3320 •
y	F4	3600 • /7	•	3280 •
ø	F4	3020 • /9	•	3280 •

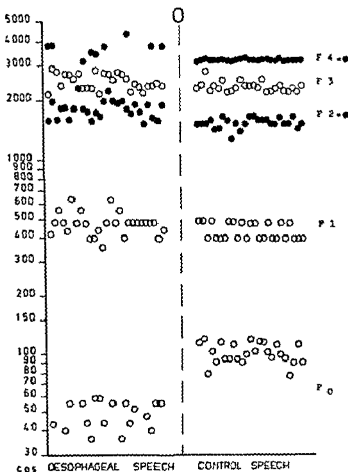


Fig 13 Frequency of F_0 and formants F 1, F 2, F 3 and F 4 for the vowel o The dots and circles forming a vertical line represent the fundamental tone and formants of one test subject

F 4 was identified somewhat more frequently in front than in back vowels When the frequency figures for the laryngectomees are compared with those for the controls, the former are found to be consistently higher and the difference to remain approximately unchanged — on an average 460 cps — irrespective of the vowel concerned. The graphic representation of F 4 in figure 5, and the corresponding control diagram, show roughly horizontal lines

The individual results for F 4 are given separately for each vowel

C. Diphthongs

The thirteen narrowing diphthongs *(ai, ei, oi, ui, yi, ai, oi, au, eu, iu, ou, ay, oy,)* and three opening diphthongs *(ie, uo, yo)* and the vowel combinations *ey* and *iy*, to be considered as diphthongs, have already been analysed above.

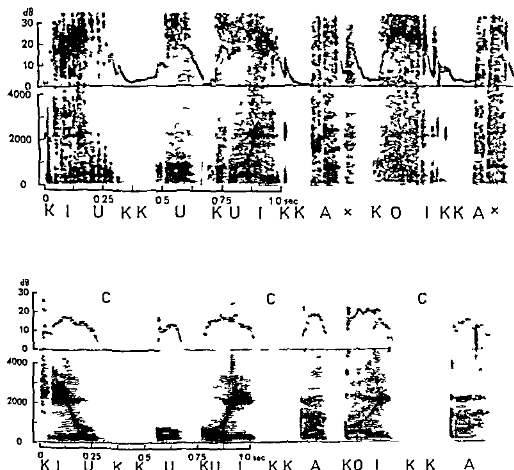


Fig 14 Spectrographic analysis of the diphthongs ɪu uɪ and oɪ in the first two ɪ (with the highest F2) adjoins u (with the lowest) As F1 shifts almost linearly from one vowel to the other F2 performs a very marked formant glide which is shown by a dotted line When there is a considerable rise in the F2 of u a distinction between uɪ and oɪ cannot always be made Cf corresponding control sonagrams (C) (x sound of air intake into *oesophagus*)

The diphthongs are vowel sounds which in the course of their duration change acoustically with changes in the position of the tongue and lips so that each of them produces a distinct pattern and thus oesophageal speakers did not find it more difficult to pronounce diphthongs than single vowels This might conceivably be due in part to Finnish vowel harmony which presupposes that a word contains either only front vowels or only back vowels However, two front vowels *e* and *ɪ* may be combined also with a back vowel and it is here that the maximum formant transitions are observed. The greatest such transition occurs in the diphthongs *ɪu* and *uɪ*, where *ɪ*, having the highest F2 adjoins *u*, with the lowest F2 (Fig 14) F1 shifts almost horizontally since F1 of *ɪ* is markedly higher in laryngectomees The

glide of F 2 in the diphthong *iu* is not equally distinct as in *ui*, where the initial back vowel makes it easier to start the voice Yet it is worth noticing that the F 2 of *u* in laryngectomees was 720 cps, thus being 90 cps higher than in the controls Thus the glide of F 2 in the diphthongs *oi* and *ui* may be approximately similar, the acoustic difference depending upon F 1 (Fig 14) Indeed it is not always possible for the ear to distinguish these two diphthongs, as already stated in the preceding chapter as far as the single vowels *o* and *u* are concerned

This also applies to *ou* and *uo*, which are often very difficult to distinguish from double *o* because the formant glides almost linearly from one vowel to the other In favourable conditions, however, the F 2 of an *o* preceding or following *u* can reach even very high values, more than 1000 cps, and the acoustic result improves as the difference between F 2 of *u* and *o* increases, the latter retaining the high level already achieved In this way a difference of sorts is produced between the F 2 values for *o* and *u*

As might be expected, the results as regards the other diphthongs were not in line with those obtained in analysing single vowels

Irrespective of the vowels of which it is made up, a diphthong reaches maximum intensity at its temporal middle point, thus showing an almost symmetric curve, as is apparent from the sonagrams of diphthongs The intensity curve does not differ essentially in the control cases

D Mutual intensity variation of formants (F1—F3)

Study of the momentary sound spectra of vowels, i e sections, shows that intensity generally diminishes with increased frequency unless this phenomenon is levelled by the above described possible noises favouring high frequencies

The formants, seen as horizontal peaks, also lose intensity in the higher frequencies Thus the dB value for F 1 is greater than that for F 2, and *that for F 2, in turn, greater than for F 3 (Fig 15, 1 and 2) However, in* laryngectomees F 1 and F 2 may occasionally have the same intensity (Fig 15, 3), or the latter may even be of greater intensity (Fig 15, 4) F 2 and F 3 may also be of equal intensity (Fig 15, 4) or the latter even stronger (Fig 15, 5), and — extremely rarely — all three formants contain the same intensity (Fig 15, 6)

When the mutual average differences in dB between the lowest three formants of each vowel are determined, taking account also of the difference (in dB) arising between F 1 and F 3, a result is obtained which is clearly consistent and correlated with the frequency of the lowest two formants in spite of apparently being sporadic (Table 7)

According to the various amplitudes of F 1—F 3, the back vowels assume the order *u o, a,* which corresponds to the increase in their F 1 and F 2 frequencies and the position of the tongue in relation to the palate For

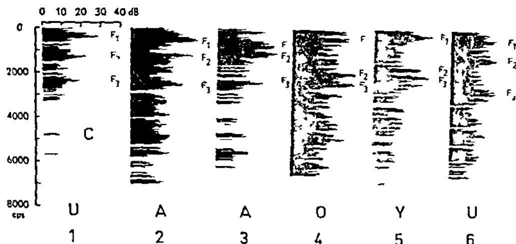


Fig 15 Spectrographic section analysis of possible intensity variations of formants 1,2, and 3 (in relation to each other) The frequency vs intensity display (a section over 30 msec period) is portrayed, over an intensity range of 35 dB Section 1 shows an ideal laryngeal voice with formant peaks decreasing in intensity towards higher frequencies, the other sections display different possible formant intensity variations apparently of sporadic nature, in oesophageal voice

F 2 and F 3 the difference is considerably bigger, and almost equal in the case of *u* and *o* So the fact that F 2 approximates F 3 reduces the intensity of the back vowels

On the basis of the different intensities of F 1 and F 3, the respective order of the front vowels is *i*, *e*, *y*, *a*, o As here the greater frequency difference appears between F 1 and F 2 — than with the back vowels — this also causes a greater difference in dB between exactly these formants, which difference is levelled as F 2 diminishes in the above vowel order and intensity also decreases Thus the F 1—F 2 gap is about twice as big in the case of *i*, *e* and *y* as the corresponding gap between F 2 and F 3 When the F 1—F 2 gap nearly equals F 2—F 3, as in *a* and *o*, the intensity values also show a close correspondence (Table 7)

TABLE 7 *Mean values for mutual intensity variations of formants F 1—F 3*

	Oesophageal speech			Control speech		
Vowels	F1—F2	F2—F3	F1—F3	F1—F2	F2—F3	F1—F3
u	6.2 dB	10.8 dB	17.0 dB	5.0 dB	11.0 dB	16.0 dB
o	6.0 »	10.0 »	16.0 »	6.0 »	8.0 »	14.0 »
a	5.8 »	7.2 »	12.0 »	4.0 »	8.0 »	12.0 »
i	10.0 »	4.0 »	14.0 »	8.0 »	6.0 »	14.0 »
e	8.0 »	2.0 »	10.0 »	7.0 »	5.0 »	11.0 »
y	6.7 »	3.3 »	10.0 »	8.0 »	3.0 »	11.0 »
ö	3.4 »	4.6 »	8.0 »	7.0 »	3.0 »	10.0 »
a	4.4 »	3.6 »	8.0 »	5.0 »	5.0 »	10.0 »

It will be seen, then, that the back vowels (chiefly *u* and *o*) usually possess somewhat greater intensity than the front vowels, and this applies to the control group too, further it is noticed that the intensity of the back vowels of laryngectomees exceeds that of the controls while the reverse is true as regards the front vowels

It is clear that F 2, because of its mid position, and reflecting as it does the position of the ridge of the tongue in relation to the palate, affects the intensity so that it decreases in the back vowels with rising F 2 and increases correspondingly in the front vowels.

The control values do not differ essentially from the above The results only are more evenly distributed, and the differences — though similar in nature — are not so big as in the laryngectomees Thus the vowels in the control cases could be placed in the same order according to intensity

3. Analysis of Finnish consonants

A. Vowel-like sounds j, v, h

Reading the *j*

The acoustic pattern of the palatal semivowel *j* bears most resemblance to that of *i* Being of fairly long duration, *j* is extremely clearly defined in the speech of all laryngectomees Of special interest is the glide of both F 1 and F 2, the latter in particular

When the back vowel *a* precedes and follows *j*, F 1 is found to glide on an average 400 cps downwards at the middle of *j* temporally and then to rise again to its starting value F 1 here, at its lowest point, has reached the variation area of the F 1 of *i* At the same time F 2 has risen on an average 1200 cps and is now in the corresponding area for F 2 of *i*, and then is restored to its starting position (Fig 16)

In the *j* influenced by the »darker» back vowel *u*, F 1 does not change to any marked degree since — as stated in the preceding chapter — the F 1 averages for *i* and *u* in laryngectomees are fairly near one another, 332 cps and 358 cps F 2, on the other hand, shows a considerable curve rising on the average to 2400 cps from the *u* mean, 720 cps (Fig 17)

In the absence of any Finnish word with *i* adjoining *j* on each side or of any word with some other front vowel following the *j*, the test word PIIJU was used Here, too, there were no appreciable changes in F 1 F 2 also shifts fairly linearly the mean for *i* was as high as 2520 cps Thus the glide typical of semivowels could not develop it is not found in this test word until the *u* is reached that follows *i* (Fig 18)

In the laryngeal voice the *j* has a noise concentration area in the range of 2100—6800 cps Though it was generally difficult to define this area because

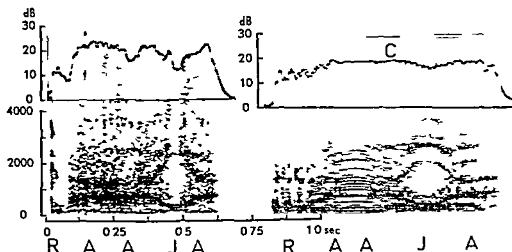


Fig 16 Spectrographic analysis of the vowel-like sound ȷ When the back vowel ɑ adjoins ȷ on both sides, F 1 is found to glide on an average 400 cps downwards in the temporal mid position of ȷ and then to regain its starting value F 1, when at the lowest frequency level, reaches the variation area of F 1 for ɪ Simultaneously F 2 shows an average increase of 1200 cps and occupies the corresponding variation area of F 2 for ɪ from here it is restored to its starting position. In the control group (C) the F 2 glide is not so sharp Intensity in ȷ is on an average 10—12 dB below the level of the preceding vowel In the control group the decrease in intensity is only 5—6 dB

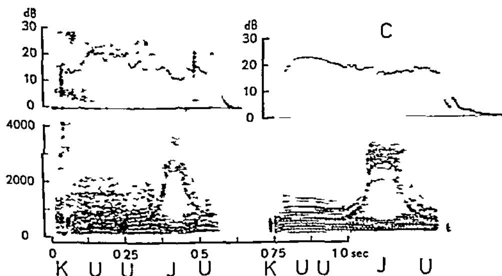
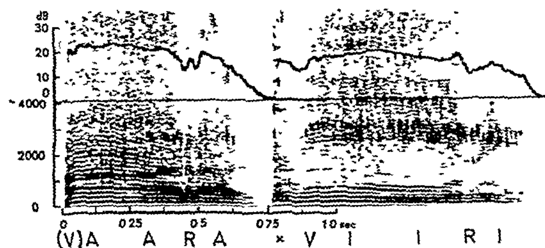
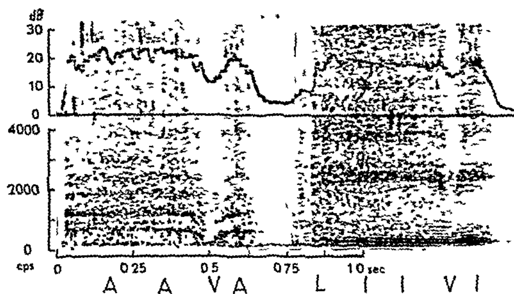
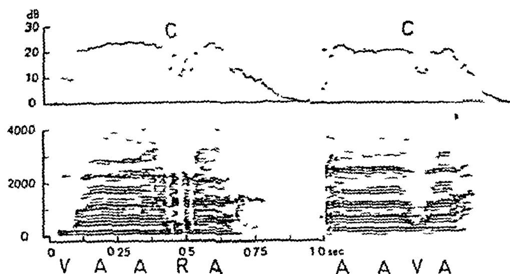


Fig 17 Spectrographic analysis of the vowel-like sound ȷ F 1 of the ȷ influenced by the back vowel u does not vary appreciably the mean F 1 values of the laryctomees are almost similar to those of the controls F 2 on the contrary shows a marked curve, rising on the average to 2400 cps In a comparison with the controls, attention is aroused especially by the difference in duration and intensity of ȷ


dB
30
20
10
0
4000
2000
0
0
0 25
0 5
0 75
1 0 sec
(V)A A R A × V I I R I


dB
30
20
10
0
4000
2000
0
cps
0
0 25
0 5
0 75
1 0 sec
A A V A L I I I V I


dB
30
20
10
0
C
C
4000
2000
0
0
0 25
0 5
0 75
1 0 sec
V A A R A A A V A

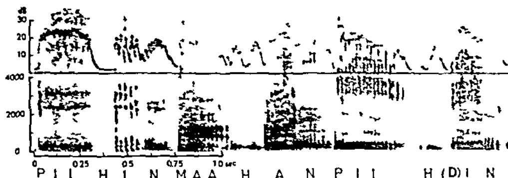


Fig 20 Spectrographic analysis of the voiced medial *h* mostly substituted for by a pause (PIIHIN) or by a noise from the tracheostoma and subglottis (MAAHAN) At the end of such a noise there often occurs the noise of a stop sound resembling an explosion i initiates the vowel that follows the *v* (PIIH(D)IN right)

level as in the adjacent sounds but are correspondingly weaker (Fig 21) However F 3 is not identifiable throughout *h* as shown in the section

Comparison with the control group shows that when recognizable the formants of *h* had higher frequency positions in the post laryngectomy group The result is in full agreement with formant variations noted in vowels

The intensity of voiced *h* is very weak Except for those cases in which *h* is omitted and has no intensity whatever, the »formant *h*» was found to be on an average 15—17 dB below the intensity level of the preceding sound The noise from the tracheostoma clearly adds to the intensity in laryngectomized cases in the controls the corresponding decrease was 20 dB The intensity of the tracheostoma noise substituted for the *h* is always of very marked degree and only 10 dB short of the general level

B Liquids l, r

Reading the *l*

In the apico-postdental lateral *l* the most characteristic energy concentration area of formants has a fairly high frequency position about 2000—3200 cps Below this there are two weaker formant areas a higher one at 1000—1200 cps and a lower at 400—900 cps

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Fig 19 Spectrographic analysis of the fricative *v* which often remains unpronounced when in initial position ((V)AARA) or follows a subglottic sound being in a way a medial *v* (VIIRI) its acoustic pattern is very good There is no formant glide however which in medial *v* is extremely clearly recognizable (AAVA, LIIVI) Intensity decreases by 8—12 dB independently of the vowels influencing the *v* the original level being reached on termination of the sound In the control group the fall in intensity during *v* is 10—12 dB (C) (x sound of air intake into oesophagus)

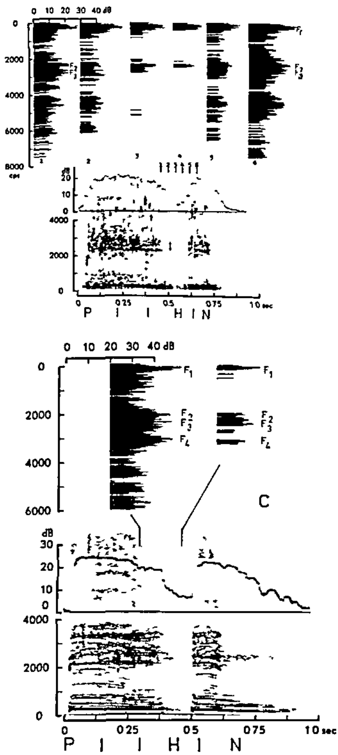


Fig 21 Spectrographic analysis of the voiced medial *h* having almost the characteristics of the laryngeal *h* F1 and F2 of the adjoining vowels during the *h* are at the same frequency level but of weaker intensity In the corresponding control sonagram (C) all four formants are clearly identifiable at the beginning of *h*

On the basis of auditory observations, the initial *l* of oesophageal speakers contains a flap resembling in type a *t-d* explosion, which as it were delays the energy explosion in the pseudoglottis, and after this has occurred, causes difficulty in the interpretation of the aural pattern of *l* (Fig 22, LUUKUT, LÖIKÖ) It is found that the energy is unevenly distributed up to the highest frequencies, and owing to this, the limits of the concentration areas are difficult to define In most cases, and most clearly, however, the range 1500—3400 cps is distinguished, which thus spreads over an extensive area, the lowest energy components being weaker The *l* is not influenced by the vowel following it

The medial *l* is produced in more favourable conditions oesophageal contraction is already present and vibrations of the pseudoglottis have reached an even rhythm All of the energy concentration areas mentioned above are recognizable as follows In the *a*- and *u*-coloured *l* the lowest area is 160—480 cps but in the *l* influenced by *i* it only rises to 320 cps (Fig 22, JAALA, SIILI, KUULU) This is not due to the low F 1 of *i* — in laryngectomees almost identical to the F 1 of *a* — but to the high frequency position of F 2 of *i*, because of which there is no »combined action» of F 1 and F 2 The next energy concentration area is most distinct and relatively of the greatest intensity when influenced by *a*—a fact essentially due to the favourable frequency level as it follows the F 2 of *a* without any marked formant transition The area is at 1200—1440 cps (Fig 22 JAALA) The influence of *u* causes the above energy concentration to appear more weakly and the average frequency range is slightly lower, or 960—1360 cps, which shows the same relationship to the F2 of *u* as, in the *l* influenced by *a*, to the F 2 of *a* (Fig 22, KUULU) After *i* this energy concentration area is entirely lacking, this may also be accounted for by the extremely high frequency position of F 2, which does not allow a formant transition sufficiently rapid for the level here required (Fig 22, SIILI)

The highest and most characteristic of the formant areas of *l* is most easily recognizable when the *l* has an *a*- or *u*-like colouring, it was possible to define its average range as 2560—3000 cps In the *l* influenced by *i*, however, this area too is very weak and its limits hard to identify by auditory observation, even in a performance relatively free from noise While the lower limit is about the same as in the *l* influenced by *a* and *u*, the high limit is clearly higher and varies between 3200 and 3800 cps (Fig 22, SIILI)

When temporally prolonged, the *l* becomes clearer in acoustic pattern thus analysis of the double *l* caused least difficulty and yielded the most definite result. The lowest energy concentration rises evenly up to 640 cps when *l* is influenced by *a* and *u*, and it is sometimes possible, in both of these cases, to distinguish at 480 cps a narrow concentration area of high intensity (Fig 23, TALLAT, TULLUT) In the *l* influenced by *i* the lowest area is lower, extending upwards to the just mentioned limit, 480 cps At times a reinforced stress is found here also, occurring at 320 cps (Fig 23, PILLIT) The middle formant area is at 1200—1680 cps independently of the preceding

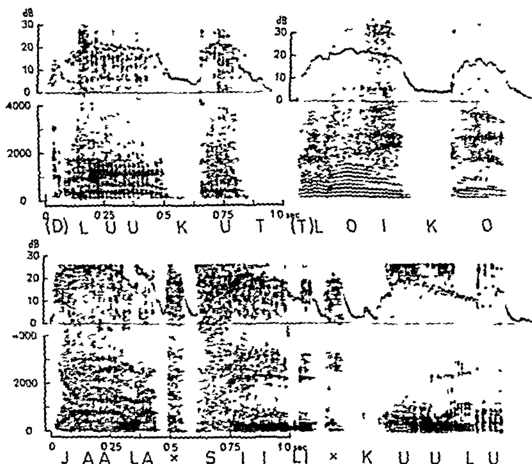


Fig 22 Spectrographic analysis of initial *l*, the place of which is taken by a plosive explosion of *d*- or *t-type* ((D)LUUKUT, (T)LÖIKÖ) Below is seen the medial *l*, as influenced by *a*, *u* and *i*, and produced in more favourable phonetic conditions (JAALA, SIILI, KUULU) During this latter *l*, intensity is usually found to decrease about 8—10 dB from the level of the preceding sound Fig 23 shows the initial and medial *l* in a control test (x sound of air intake into oesophagus)

vowel The highest formant area of the double *l* does not differ to any appreciable extent from the corresponding area for the single *l* It should be noted, however, that the lower limit, which is very constant, is 2400 cps in the case of the *l* influenced by *a*, *u* and *i*, and thus is lower than the corresponding figure for the single *l*. The upper limit varies from 2800 to 3040 cps in the *l* influenced by *a* and by *u*, and is on an average 3300 cps when *l* has *i*-like colouring (Fig 23, PILLIT)

Intensity variations during the single *l* do not differ to any marked degree from the control results During the sound *l* intensity falls obliquely about 8—10 dB from the preceding level, a fall which exceeds the corresponding figure for the controls by about one-third After the conclusion of *l*, intensity does not in general attain its original level but stays about 3—5 dB below it — *a finding common in the control group*

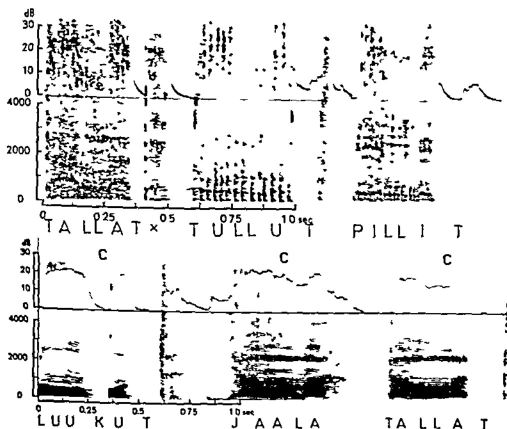


Fig 23 Spectrographic analysis of double *l*, where the longer time given to the sound makes the acoustic pattern clearer Intensity is found usually to remain almost horizontal 5—8 dB from the original level (TALLAT) If fundamental vibration is fairly slow, the intensity of double *l* decreases continually and does not even reach its original value in the following sound (TULLUT, PILLIT) In the laryngeal voice the double *l* remains unchanged in intensity, about 5 dB below that of the preceding sound (See control, TALLAT)

too The double *l* usually has an almost horizontal intensity curve 5—8 dB above the original level, and this is occasionally reached even after termination of the *l* A loss of a few decibels is common both in oesophageal speakers and in the control group But if the vibration of the fundamental is comparatively slow, intensity decreases continuously in the double *l* and does not reach the original level in the following sound (Fig 23, TULLUT, PILLIT)

Reading the *r*

The apico-alveolar tremulant *r* is a noise-formant consonant, which contains at least two flaps These, and the stream of air emitted towards the alveolar ridge give the sound the character of noise

The energy concentration areas typical of *r* in normal speech totalling three, are fairly low and also have fairly low frequency positions The lowest

of these ranges is 250—500 cps, the next 1000—1800 cps, and the highest 1760—2480 cps

The first-mentioned, lowest energy concentration area corresponds to the F 1 of vowels, being a direct extension of it, whereas the next one is correspondingly associated with F 2 and the highest with F 3 Depending on the influence of the adjacent vowels, formant transition occurs, and this changes the inner colouring of the *r* to some extent

Above these formant areas, there is a considerably weaker noise concentration area, which is caused by the alveolar ridge

The initial *r* was difficult to make for the oesophageal speakers it was either wholly absent or contained only one noticeable apico alveolar flap (Fig 24, RIISI, RUUSU) The acoustic pattern also otherwise remained incomplete formant energy concentration areas were scarcely identifiable or were absent On auditory observation this produces the impression of a sudden subglottic explosion, which is difficult to recognize as *r* because it occurs alone Indeed, the recognition of *r* is only possible in context

A few oesophageal speakers, it is true, combined such a subglottic explosion with an *r* of weaker intensity, which in a way becomes a medial *r* (Fig 24, RAAJA) This is so rare that it evidently requires, among other things, an extremely favourable moment of phonation

The medial *r*, having on the average 3—4 flaps, is acoustically fairly complete compared with the initial one, and it is heard distinctly in spite of the slow movement of the tongue The acoustic pattern becomes still more distinct in the double *r*, where the apico-alveolar flaps — on an average six — articulated at a uniform rate, are most favourable from the point of view of auditory observation

The level of the lowest energy concentration area of the *r*, as made by oesophageal speakers, is determined by the frequency position of the F1 of the preceding vowel, as follows when influenced by *a*, energy concentration extends on an average up to 680 cps, but when influenced by *u* or by *i* — F 1 of *u* and *i* being almost the same and about 400 cps lower than F 1 of *a* — it generally only reaches as far as 560 cps (Fig 24, VAARA, KUURU, VIIRI)

In the double *r* this no longer occurs so distinctly the longer duration, though only 6—8 secs, allows time for intensity to become level and in this case to rise to the level produced by »pure» articulation Thus the lowest energy concentration forms a curve reaching as high up as 880 cps before the stage of explosion, when intensity again begins to decrease (Fig 25, PARRAT, MIRRIT)

The next energy concentration area of *r*, a distinct zone about 160 cps broad, is influenced by the F 2 of the preceding vowel in such a way that, when this formant is very high, in the case of *i*, energy concentration amounts to about 1600 cps, after *a* to 1440 cps, and after *u*, where it varies most, to 800—1280 cps (Fig 24, VAARA, KUURU, VIIRI) The single and the geminate *r* did not differ in this respect

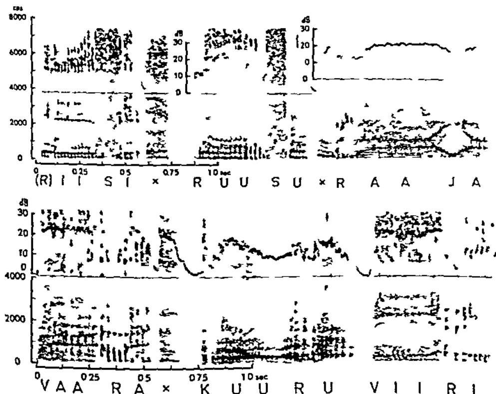


Fig 24 Spectrographic analysis of the tremulant *r* in initial position it can be totally absent (RIISI) be dependent upon one ap co palatal flap (RUUSU) or — extremely rarely — follow a subglottic sound (x) (RAAJA) being of weaker intensity than it but containing a greater number of flaps

Below is shown the medial *r* acoustically fairly complete compared with the above and having 3—4 ap co alveolar flaps Intensity depends upon the mutual distance of these movements with increased distance it falls 7—12 dB from its maximum Even before this there has been a decrease of about 10 dB from the level of the preceding sound which decreased level is reached by the maxima of the flaps

The highest of the three energy concentrations is not nearly always distinctly recognizable in the single *r* (Fig 24) but in the double *r* it is mostly very clearly discernible similarly as the preceding concentration area it occurs as a narrow zone 160 cps in width at about 2400—2500 cps (Fig 2[illegible] PARRAT MIRRIT)

The greatest difference compared with the control values occurs in the pharyngeal and lowest energy concentration of *r* its maximum was found to be 680 cps and for the geminate *r* as much as 880 cps The former [illegible] its control value by 200 cps The other two energy concentrations [illegible] did not differ from those obtained in the controls

The alveolar friction of weak intensity proved difficult to define [illegible] it was obscured by *noise* from the tracheostoma subglottis [illegible] bled to some extent its absence could not be clearly demonstrated [illegible]

The *r* varies widely in intensity (all figures) and this [illegible]

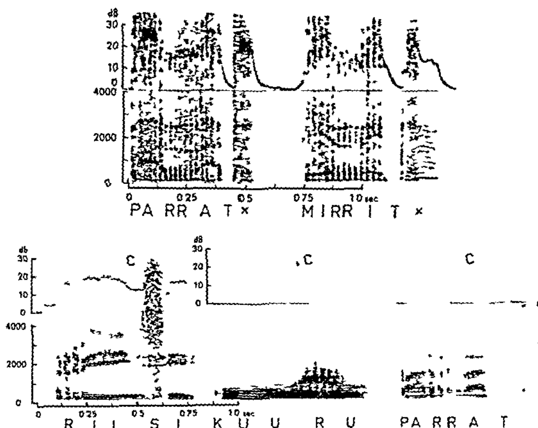


Fig 25 Spectrographic analysis of double *r*, which has sufficient duration for the energy concentration areas to develop unhurriedly Alveolar noise of weak intensity, cannot be definitely demonstrated nor can it be shown to be absent it is obscured by the noise from the tracheostoma and subglottis which it resembles to some extent As in the case of the single *r*, the intensity in the double *r* declines about 10 dB from the level of the preceding sound, but, since the distance between the apico alveolar flaps and the range of their variation remain unchanged, the maximum-minimum difference is only about 5 dB The control *r* below (C) also retains its range of variation of c 5 dB irrespective of its position, and its total intensity remains unchanged and is unaffected by the duration of the sound (x sound of air intake into oesophagus)

on the mutual distances between the apico alveolar flaps in such a way that, as this distance lengthens intensity decreases by 7—12 dB from the maximum occurring at that phase of a flap during which intensity reaches a maximum to be restored nearly to its previous level before the same phase of the next flap begins Before this, intensity has already dropped about 10 dB from the level of the adjacent vowel, which reduced level the maxima of the flaps reach The intensity of the double *r* also falls about 10 dB from its original level the degree of difference between individual flaps remaining fairly constant and the maximum minimum difference smaller than above, about 5 dB In the controls the *r* retains its range of variation of about 5 dB independently of its position and its total intensity also remains unchanged whether the *r* is single or double

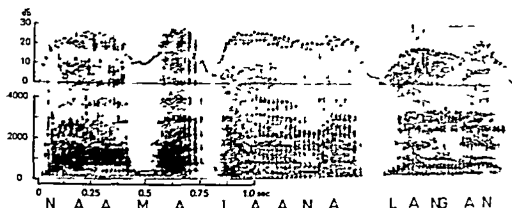


Fig 26 Spectrographic analysis of the nasal sounds m, n and η m during the transition causes a downward glide in F 1 and F 2 of the preceding vowel and the opposite phenomenon in the same formants of the following vowel During the transitional phase n produces a downward shift of F 1 and an upward shift of F 2 of the preceding vowel if permitted by the F 2 of that vowel, and the reverse phenomenon in the following vowel. η shows most correspondence with the medial n F 1 has a wider range than in the case of other nasals Intensity during all the nasals is 6—12 dB lower than for the adjacent sounds to increase after termination of the nasal to the original value

C. Nasal sounds m, n, ng

Reading the *m*, *n*, *η*

Being vowel formants proper, F 1 and F 2 are of secondary importance in the nasals themselves but perform a definite transition decisively influencing the acoustic pattern, in the preceding and following vowel. Thus the initial *m*, during the transition to the following vowel, causes an upward glide of F 1 and F 2, whereas the medial *m* causes the opposite phenomenon in the preceding vowel The initial *n* causes shifting of F 1 upwards, and of F 2 downwards, if the F 2 of the vowel that follows *n* permits this When *n* is in medial position, the F 1 of the preceding vowel falls and F 2 rises subject to the above condition as regards F 2 In the case of *η*, approximately the same phenomenon occurs as in the medial *n* but is often less distinat because the F 1 area is broader than above (Fig 26) Thus, if one covers the nasal sound in the sonagram, it is possible in the transition phase of the F 1 and F 2 of the preceding or following vowel to say which of the nasals is concerned in each case F 3 is not affected by the proximity of a nasal.

In oesophageal speakers the pharyngeal resonance corresponding to the lowest vowel formant of nasals occurs in those nasals influenced by *a* and *u* in the area representing the mean frequency 240 cps This being so, the continuity of the F 1 of the adjacent vowels is no longer demonstrated linearly in the nasal itself

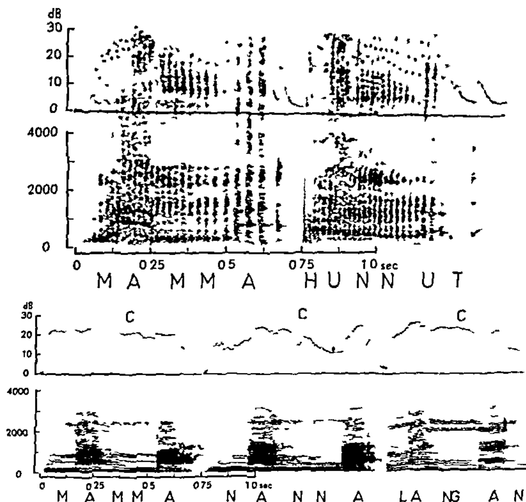


Fig 27 Spectrographic analysis of double *m* and *n* Because of their longer duration the acoustic pattern is more distinct than that of the single nasals but no essential difference appears *The increased duration of the sound and the possibly slow vibration of the* pseudoglottis tend to diminish intensity more distinctly than in the single nasals *The tendency for intensity to fall off is apparent also from the control sonagrams below (C)*

The next, broad and strong energy concentration area, corresponding to the F 2 of the adjacent vowels occurs at 960—1840 cps This is not yet a nasal formant proper but evidently due to epipharyngeal resonance

At the highest frequency level there are two fairly broad energy concentration areas side by side The mean for the lower one is 2160 cps and the range 2080—2560 cps while for the upper one these values are respectively 2800 cps and 2720—3040 cps

In a nasal influenced by *i* the lower of the above-described areas is approximately at the level of F 2 and the impression is then easily conveyed that *the energy concentration of the vowel concerned continues to the area of the* adjacent vowel This is not the case, however, as seen in the nasals influenced

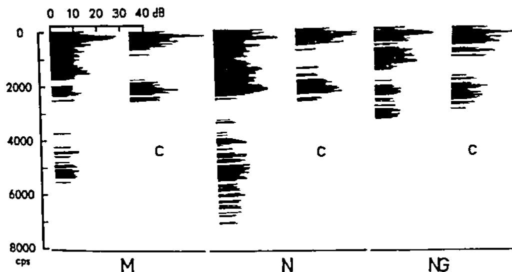


Fig 28 Spectrographic analysis of the anti-resonance found in nasals and appearing in the sections as »gaps» These are usually narrower than in the controls (C) and clearly have higher frequency positions It is seen that the »gap» is broadest in the bilabial *m* narrower in the apico dental *n*, and narrowest in the dorso-velar *ŋ*

by *a* and *u* and having low formant values A nasal thus remains unchanged in nature independently of the vowels it is combined with or of the vowel following it.

The acoustic pattern of the double *m* and double *n*, because of their longer duration, is clearer still than that of the single sounds yet it is in no way different (Fig 27, MAMMA, HUNNUT)

Besides the formant transition and formant resonances playing an essential part in the acoustic identifiability of the nasals, there is also another phenomenon, characteristic of the nasals alone and directly contrasted with the formant resonances This is the anti-resonance produced by the oral cavity Owing to it, the nasopharyngeal vibration at certain frequencies disappears In the sonagram this is visualized as blank spaces, and in sections from the temporal mid point of the nasals this phenomenon is mostly very clear in the controls (Fig 28) The bilabial *m* shows the broadest area of this kind, the apico-dental *n* a narrower one, and the dorso-velar *ŋ* the narrowest In the laryngectomees, the tracheostoma noise may in part obscure these »gaps», so that the pattern is not fully distinct Yet the intensity of the noise is generally 3—5 dB less than the critical energy concentration areas, and so the acoustic pattern and intelligibility are maintained In the laryngectomees no damping areas could be precisely determined In *ŋ*, however, where the altered conditions in the hypopharynx are most perceptible, the rise of the damping area under favourable conditions is found to be about 400 cps because of decreased size of the cavity, on the other hand the area of attenuation is

also 250—300 cps narrower than in the controls, which fact levels out some of the difference The damping is further narrowed by the width of the nasal resonance, referred to above

The results were compared with those obtained for the control group The first observation of interest was the mean pharyngeal resonance 240 cps, the normal value being for all nasals 160 cps The result was to be expected it corresponds *with the finding already made in back vowels, viz* that F 1 tends to show higher than normal values because of diminution in cavity volume Epipharyngeal vibration, 1440 cps, also exceeds the control value (1200 cps) and accords with the changes in F 2 of vowels However, the highest formants, generated in the nasal passages, show a broader frequency area than the controls The energy concentration area of the laryngectomized group, 2160 cps, corresponds to 2240 cps in the control group, and for the highest area these figures are respectively 2800 cps and 2640 cps The difference here is 640 cps for the postlaryngectomy group and 400 cps in the controls

Intensity during all the nasals is 6—12 dB lower than in the adjacent sounds, to rise again to almost its original value, sometimes to within 2—3 dB of it In the double *m* and *n* the case is similar but less pronounced, so that the minimum intensity — of the same amount as above — is not reached until the terminal portion of the sound In the controls the intensity shows a similar curve, which is unaffected by *a* , *u*- or *i*-like colouring

D) Fricative sounds h, s

Reading the *h*

The initial, voiceless spirant *h* follows the same general lines as its voiced equivalent *it is frequently omitted or mostly on auditory observation is* substituted by a noise resembling the explosion of *k* (Fig 29) It can also be replaced by the noise from the tracheostoma-subglottis

Occasionally, however, and evidently at a favourable moment of phonation, an initial *h* of almost normal pattern is found, even showing a distinct, though weak, F3 (Fig 30) It is probable that a maximal amount of air in the oesophagus offers the best conditions for making the *h* successfully and for the release of the required »waste air», the formant structure can then build up according to the requirements of the succeeding vowel, the tongue channel being in advance in the correct anatomic-functional position The *h* perceived by the ear is further reinforced by the pause of 0,01 secs, which commonly *precedes the following vowel*

If the initial is not pronounced the following vowel attains its greatest intensity immediately at the onset of phonation When some explosion of stop type is substituted for *h*, the intensity may be weaker than or the same

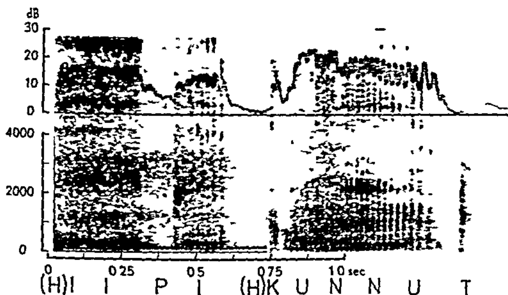


Fig 29 Spectrographic analysis of the initial voiceless *h*, frequently omitted ((H)IIPI) or perceived by the ear as noise resembling an *k*-like explosion ((H)KUNNUT) In the absence of *h*, the following vowel reaches its maximum intensity immediately at the onset of phonation. When some explosion of stop sound type takes the place of *h*, intensity can be less than or equal to that of the following vowel.

as during the vowel that follows, but always when *h* is acoustically more highly developed, *its intensity is remarkably* slight, differing 10—15 dB from the level of the following vowel

Reading the *s*

The medio-alveolar, voiceless sibilant *s* in *Finnish is associated* with fairly thick friction, as the tongue groove is here very broad. The characteristic noise concentration areas, two in number, are very highly located though it is evident that the oral cavity reinforces the *s* to a slight extent from 1000 cps upwards The first actual noise concentration area begins at 2500 cps and continues, weakening in *intensity, up to 3000* cps Here a new noise concentration area begins which also decreases in intensity but continues up to about 8000 cps These noises are of alveolar-teeth ridge origin

In initial-*s* words, laryngectomees mostly substitute a subglottic noise for the *s* or that noise may be *immediately followed* by an *s* in a way of medial character (Fig 31)

It is not nearly always possible to differentiate separate noise concentration areas Often a single uninterrupted white noise is present, which — when reinforced in its upper portion from about 4800 cps upwards — rises to the upper limit of the sonagram and with great probability even *continues far* beyond it (Fig 24 RIISI RUUSU)

Fig 30 Spectrographic analysis of an initial, voiceless *h* with almost perfect acoustic pattern A section of the initial noise of weak intensity reveals three formants of *h* influenced by *i* In the later section, at the phase when *i* becomes level, these formants are stronger A corresponding control result is seen on right (C)

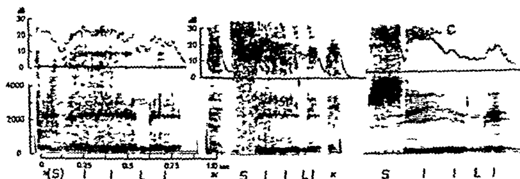


Fig 31 Spectrographic analysis of the voiceless fricative *s*, which in initial position is replaced by a noise from the tracheostoma-subglottis (x) (first section) or occurs *after the noise in «medial position» (second section)*, here there is an unbroken noise concentration area reinforced in its upper portion. This is typical of oesophageal speakers At right, control sonagram of initial *s* (C)

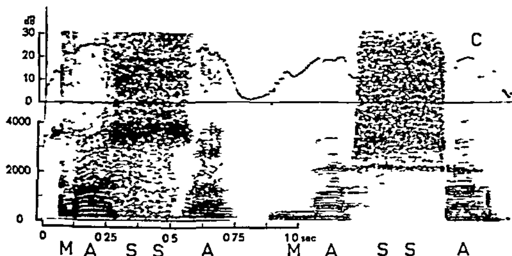


Fig 32 Spectrographic analysis of double *s* where the long duration of the sound reduces other noise and renders the aural pattern clearer Of the two noise concentration areas of *s* the lower one starts at 3200—3600 cps and the upper at 5200—5400 cps The control sonagram on right represents considerably lower frequency values

The lower noise concentration area typical of the *s* is obscured to such an extent by other noise, chiefly by tracheostoma noise, that it cannot possibly be identified. To the extent that isolated energy concentration areas are present — sufficiently distinctly only in the case of the double *s* — whose long duration evidently reduces other noise and so makes it possible for characteristics to show up, the lower of them occurs at 3200—3600 cps (starting higher than the corresponding control value) and the upper one correspondingly higher, starting at 5200—5400 cps In the laryngectomees, then, the differences between the initial frequency values for the areas concerned are greater than in the controls (Fig 32)

There is often a pause of 1—2 secs between the *s* and the sound preceding it, during the pause the tip of the tongue assumes its groove-shaped medio-alveolar position Intensity decreases for the duration of the pause about 10 dB from the level of the preceding sound to regain that level at the middle portion of *s* This also applies to oesophageal speakers when such a pause occurs, to the extent even that the intensity of *s* exceeds the level of the preceding sound by 5 dB (Fig 24, RUUSU) Obviously oesophageal contraction has increased during the pause, and when the subglottis reopens to make the *s*, this occurs at greater intensity than before

There is not always such a pause in oesophageal speech If not, the single *s* has its horizontal intensity both before and during the *s* (Fig 24, RIISI) It has been found that the pause preceding *s* is commonly absent in the double *s* Yet there is the difference that intensity decreases about 10 dB — as in the presence of a pause — from the level of the preceding sound. Because of the prolonged pronunciation, it seems, the intensity no longer has

power to rise during the double s but continues horizontally to the succeeding sound, where it is restored almost to the initial value (Fig 32) An *s* of this kind on auditory observation is fairly thick, resembling a palatal sibilant and containing also much postalveolar noise which fills the gap preceding *s* referred to above

E) Plosives p, t, k, d

Reading the *p, t, k, d*

The bilabial *p*, the dento-labial *t*, and the velar *k* are the voiceless stop sounds, which being noise-formant consonants, are very difficult to analyse It is known on the basis of Sovijarvi's studies (with automatic sound analyser) of *p*, *t* and *k*, influenced by *a*, *u* and *i*, that *p* has two strong noise concentration areas at 360—720 cps and 1120—2850 cps, *t* also two at 250—2000 cps and 2200—2800 cps, while as distinguished from the others *k* has only one noise concentration area at 900—2250 cps

The explosive noise of a voiceless plosive is of so high speed, in laryngectomees on an average 0 02 sec, and requires so high an oesophageal pressure, that the energy concentration is here distributed more or less evenly up to 8000 cps

This being the case, these noise concentration areas cannot be reliably determined in the sonagram, and it is not even possible always to say whether there is one or several However, in the identification of non-aspirated plosives, sound shift is of importance, it causes an explosive noise of short duration to be prolonged in the first portion of the following vowel or the latter portion of the preceding vowel From the point of view of auditory observations this is of essential importance in spite of what was stated above the observation group was usually able to identify without difficulty all the plosives made by the laryngectomees *p*, being bilabial, proved the easiest both to say and to identify, and *t* followed next as it still is articulated with the tongue against the teeth The plosive *k*, because of its most posterior origin, is more easily mixed with other noise, and so remains in the most unfavourable position The result was unaffected by the position of the plosive in the word, whether initial, medial (also double), or terminal

As both energy concentration areas in *p* are very low, this is visualized as a darkness of the pattern, which weakens towards higher frequencies so that the areas cannot be differentiated and show no distinct upper limit (Fig 33 PARRAT, PURRUT)

In *t* the energy is situated higher and the energy concentration areas are farther apart mixed with noise, this is shown as a fairly distinct column, which also displays no clear limits of energy concentration (Fig 33, TAKKA, PURRUT PARRAT)

k, with one strong noise concentration area, proved more distinct than the other stop sounds the upper limit of this area could mostly be determined (Fig 33 KOIKKA, TAKKA) The average upper limit was 2400 cps a

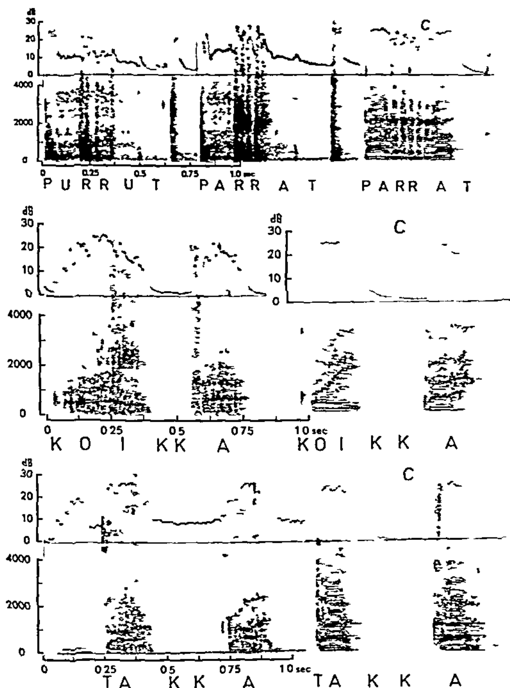


Fig 33 Spectrographic analysis of the plosives p t k The energy concentration areas of p are apparent as darkness of the pattern which grows weaker with increasing frequency (PURRUT PARRAT) In t the energy occurs lower down and the energy concentration areas are farther apart, and mixed with noise they form an uninterrupted column (TAKKA PURRUT PARRAT) k having only one energy concentration area, is more distinct than the others and it was possible to define the upper limit of this area as 2400 cps the corresponding figure for the control group being 2250 cps The lower limit is obscured by loud low-frequency noise On right control sonagrams (C)

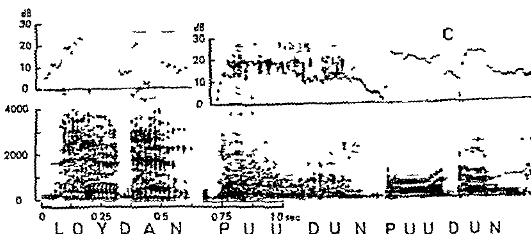


Fig 34 Spectrographic analysis of the medio-alveolar, voiced *d* Voicing is seen at about 240 cps or about 80 cps higher than in the control material. In the laryngectomized cases the duration of the voiced part is always shorter than in normal speech During the voiced part, intensity decreases by 10—15 dB, while in normal speech the decrease is less than 10 dB. *The explosion includes energy rather evenly distributed over the entire* frequency scale and no attempt was made to analyse it in detail

higher value than the corresponding control figure, 2250 cps In spite of its velar origin, the upper noise concentration limit of *k* was evidently raised owing to the diminished size of the hypopharyngeal space Because of the loud low-frequency noise it was not possible to determine whether the lower limit was also correspondingly higher

The last plosive to be dealt with is the voiced, medio alveolar *d* Some of the laryngectomees substituted *t for* it mainly because of their dialect, and indeed it resembles *t* most from the acoustic point of view Before the typical stop-sound explosion, there is in *d* one separate energy concentration area, where *is a voiced portion consisting of only low-frequency components* This portion is always of shorter duration in laryngectomees than in the controls the averages are 0 04 sec and 0 06 sec respectively The strong vibratory component of the voiced portion is at 240 cps and in the control group at 160 cps The explosion of *d* contains so much evenly distributed energy as to make a more detailed analysis impossible (Fig 34)

The intensity decreases by 10—15 dB during the voiced part owing partly to its long duration, the control value is below 10 dB During the explosion the energy usually reaches the level of the vowel preceding *d*

CINERADIOGRAPHIC RESULTS

1. Shape and location of pseudoglottis

It is the pseudoglottis that, as a rough substitute for the larynx, determines the fundamental frequency and pitch of the oesophageal voice This case material consisted of only good oesophageal speakers and auditory observation was supplemented by clinical studies of the larynx, hence it may be assumed that the pseudoglottis, as a functioning organ, is located at the oesophageal orifice

Naturally, the insertion of the cricopharyngeus, together with possible mucosal folds, determines vertically the limits within which the pseudoglottis can develop

In all six laryngectomees cineradiographically examined, a pseudoglottis of some form or another could be defined at the level of the IV—VI cervical vertebrae, in four (cases 10, 11, 12, 25) it was located in closest proximity to C VI, in one (case 15 not clearly) in the area of C V—VI, and in one (case 2) in that of C IV—V

At the time the pseudoglottis begins to form it is a relatively flat bulge in the dorsal oesophageal wall corresponding in height to about two cervical vertebrae As it bulges further in ventral direction, its base narrows vertically, so the final location will be approximately at C V—VI, or at the lower end of the space mentioned (Fig 35)

Despite the small number of cases, the level of C VI proved the most frequent location only one pseudoglottis with higher location, differed definitely in this regard (Fig 37)

The four cases with the pseudoglottis located at the same level are similar and have the appearance shown in figure 35 The hypopharynx is fairly large and the pseudoglottis club-shaped and curved obliquely downwards Further to be noted is the presence of a sagittal fold, evidently favourably completing oesophageal function, at the site corresponding to the base of the pseudoglottis, i e the ventral wall of the orifice of the oesophagus In figure 35 this appears more distinctly than in the other three of the four patients

In the fifth case at the same level the pseudoglottis was only a flat bulge in the dorsal oesophageal wall, corresponding roughly to the initial phase of its formation in the previous cases (Fig 36)

The pseudoglottis located at the level of C IV—V differed from the »general type» represented by the above four cases not only in regard to location but also to its more awkward shape Even the primary stage of this

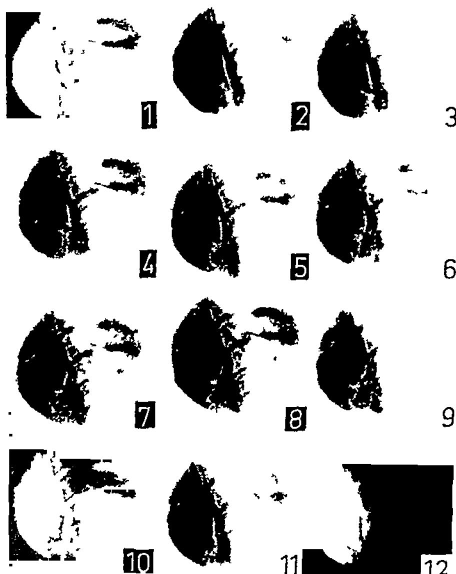


Fig 35 Selectively abbreviated sample of cineradiographic film with opaque medium (every fourth exposure included) of laryngectomized patient during phonation of the vowel *a* The pseudoglottis is club-shaped with the head obliquely downwards, located at level of C VI

pseudoglottis is different it appears as a pointed horizontal bulge, which at the terminal stage forms a thick pseudoglottis shaped like a club without a shaft (Fig 37)

The shape and function of the pseudoglottis was found to be unaffected by the colouring of the three most important vowels (*a*, *u*, *i*) made by the subjects during cineradiography

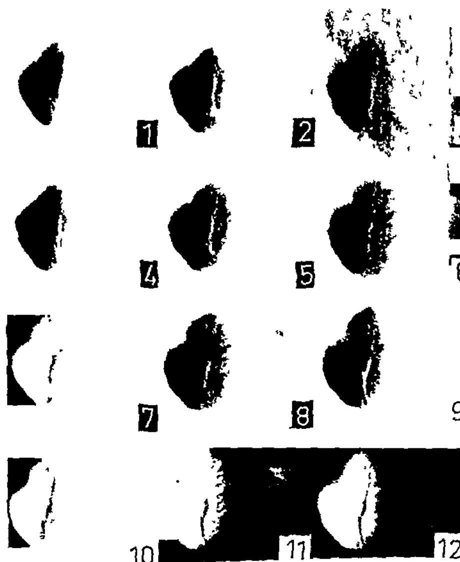


Fig 36 Selectively abbreviated sample of cineradiographic film with opaque me((every fourth exposure included) of laryngectomized patient during phonation of vowel *a* The pseudoglottis, located at C VI, is a flat bulge in the dorsal oesoph wall corresponding roughly to the initial stage of the pseudoglottis shown in *Fig* 35

2. Correlation of pseudoglottis and fundamental frequency

The fundamental frequency is definitely related to the shape and locat of the pseudoglottis, though it is greatly influenced also by *incidental* fact such as mucus and variations in oesophageal pressure, etc

When comparing the shape of the pseudoglottis, which was similar in f

DISCUSSION

By combining the results of auditory observation, basic sonagrams, and section or momentanic intensity frequency spectra, a useful general picture of the fundamental pitch and of the formant and component structure of the oesophageal voice can be obtained, as well as of other distinctive characteristics of the post-laryngectomy voice as compared with the normal voice

Fundamental pitch

The present investigation showed that the fundamental pitch of oesophageal speech is of great variety the low, at times aperiodic frequency is associated with numerous adventitious tones or overtones, to which is added the noise from the tracheostoma distributed over the entire frequency scale, reducing the intelligibility of this speech, sometimes greatly

Oesophageal voice also resembles whispering, as mentioned by Palva (1958 b) »The uniform finding in the analyses of single whispered sounds was the spread of energy into a clearly larger frequency area than was found with spoken sounds» On the other hand, oesophageal voice has certain features of hoarseness According to Nessel (1960) »The vast majority of all cases of »hoarseness» is marked by characteristic spectral criteria above 5000 cps First of all, additional (non-harmonious) noise components with definite frequency location in the upper range of the sound-frequency spectrum represent the designating features»

Damste (1958) also called attention to these factors of an oesophageal voice, stating that the fundamental *tone is often* difficult *to* determine because the frequency is low and the sound is very complex, in other words the fundamental tone is accompanied by a large number of relatively strong overtones Tato et al said of two of his 12 cases that noise did not permit the registration of tones, in only 7 was he able to determine the fundamental frequency for all the vowels studied by him

The fundamental frequency could be determined for all vowels in 18 of the 27 laryngectomized subjects in the present study In the others the noise from the tracheostoma, and especially from the subglottis, was so disturbing as to make reliable determinations impossible The mean for the laryngectomees, 50 4 cps, is at the high frequency end of the contra octave, the distance from the control mean, 104 cps, being approximately one full octave Curry & Snidecor obtained the mean frequency 62 8 cps for their laryngectomees which differed about one octave from the control

value Thus their control value must have been correspondingly higher than that obtained here

The mean fundamental frequencies reported by other observers have been fairly high in some cases, corresponding even to that of the normal male voice (Tato et al 30—60 cps, rising with training to 60—150 cps, mean 78 7 cps, Damsté (1958) 78 5 cps, Luchsinger 50—64 cps, Berg & Molenaar-Bijl, and Levin (1962) 50—100 cps, Pantyukhin 60—100 cps)

There are only a few detailed experimental studies dealing with the frequency abilities of oesophageal speakers In this respect the studies of Damsté (1958) and of Curry & Snidecor take a prominent place they supply precise mean frequency figures, about one half octave higher than those in the present study. The highest frequency reported in Damste's (1958) study was 185 cps, in Curry & Snidecor's 80 8 cps, and in the present work 72 cps The lowest frequency measured by the present writer was 32 cps, by Damsté 36 cps, and by Curry & Snidecor 17.2 cps

According to Tato, the fundamental frequency increases with training It cannot be denied that increased frequency makes speech more intelligible yet from the point of view of auditory observation relatively small differences in fundamental frequency are scarcely noticeable the intelligibility of oesophageal speech, in point of fact, is indirectly related to the various associated noise factors Likewise, the limitations of auditory observation due to the remarkably low fundamental pitch deserves notice the higher the frequency of the fundamental tone, the lower is the frequency discrimination threshold (Hirsch 1952) On this basis Stevens & Volkman (1940) present experimental evidence which clearly indicates that »in the frequency region below 100 cps the perceptual or pitch aspects of a stimulus are greatly reduced when compared with frequencies above 100 cps»

The auditory observation group did not, in fact, notice any appreciable frequency variation in the post-laryngectomy speech of one and the same case However, measurement of the fundamental frequency showed unexpectedly large variation, 3—4 tones, which was found to represent the mean variation in the individual cases In the control group this mean variation was 2 5 tones Curry & Snidecor also noted »a considerable lack of agreement between the measured (frequency) and perceptual (pitch) aspect of the low frequency speaking performances of these oesophageal subjects» In spite of the »restricted pitch range», they reported the fundamental variation in laryngectomees as 6 5 tones and in the control group as 6 3 tones This shows that, despite the possibilities present, the laryngeal voice does not vary much but even slightly less than the post-laryngectomy voice A variation of a few tones in the fundamental pitch of laryngectomees lacks practical significance, since the frequency of the fundamental tones does not even in the most favourable anatomic-physiological conditions reach the level of the normal voice

Tato et al directed interest to the possible variation in fundamental frequency in the case of different vowels, stating that o is always of higher

pitch than the others The same result was not obtained here (not with the normal voice either) the means for the various vowels showed no statistically significant differences However, the fundamental frequency of the back vowels u, o and ɑ increased in the order stated, which may bear a certain correlation to F 1 and F 2 in such a way that the fundamental frequency rises with a rise in these formants

Vowel formants

Following removal of the larynx, the base of the tongue being directly connected with the oesophagus, the vowel tract loses a portion of its most posterior resonance cavity, which becomes apparent as a rise of the mean frequency results for all vowel formants studied

In evaluating the mean formant frequencies obtained, it deserves special notice that the fundamental frequency of the oesophageal voice is about one full octave lower than the control value Keeping in mind that a rise of the fundamental note by one octave causes a 17 per cent average increase in formant frequency (Peterson and Barney, Fant 1959), the result here reached is all the more significant

The first formant

Of the back vowels, *ɑ* was the only one with a quite considerable rise in F 1 129 cps above the control value The result is probably due in part to the unrounded nature of *ɑ* and to the fact that *ɑ* is generated anatomically more posteriorly than the other back vowels In the view of Fant (1960), though F 1 is generally dependent more on the back cavity volume than on the volume of other cavities, the vowel *ɑ* is an exception its F 1 is affected equally on a percentage basis by a change in the front cavity volume and by a change of the back cavity volume It is evident that the latter cavity volume plays an exceedingly prominent part in the F 1 of *ɑ*, even though *ɑ*, as distinguished from the other back vowels, would be equally dependent upon the front cavity volume It does seem, in fact, as if exactly the *ɑ* were greatly dependent upon the back resonance cavities and the other back vowels much less so the F 1 values of these latter did not differ from the control values to any extent worth mentioning

The F 1 values for all front vowels exceeded definitely the control level, the most marked difference, 88 cps, occurring in the case of ɪ, the cavity volume was also smallest in the vowel ɪ, the ridge of the tongue being in closest proximity to the palate

The second formant

The F 2 of each of the three back vowels exceeded the corresponding control value in such a way that the difference for u, o and *ɑ* respectively was 90 cps 84 cps and 54 cps This order was to be expected since the *u*

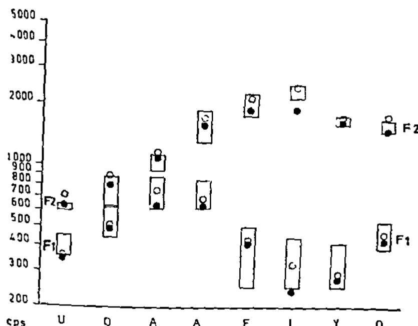


TABLE 8 *Mean F 1 and F 2 as measured for laryngectomees (o) and for control subjects (●) when placed into the variation areas measured by Sovijarvi for the same formants (□)*

presupposes the highest tongue-ridge position and thus the smallest distance to the palate, o following next in this respect, and *a* coming last

The F 2 values of the front vowels are also higher than the control readings but they do not show the same anatomic-functional order as the back vowels, however, the unrounded vowels, *i* and *e*, requiring the highest tongue-ridge position, achieved the greatest difference the former 348 cps and the latter 274 cps Fant (1960) stated that F 2 of *i* is clearly a half-wavelength resonance of the back cavity and that there is a similar but not at all so apparent tendency for F 2 of *e* to be influenced more by the back than by the front cavity The greater importance of the back cavity in the F 2 of both *i* and *e* is clearly visualized in the above-mentioned increased values in laryngectomees

For a more complete over-all conception, the mean frequencies for F 1 and F 2 were compared in addition with the results reported by Sovijarvi (1938 b) from measurements of the F 1 and F 2 variation areas of spoken, sung and whispered vowel variants

Table 8 compares Sovijärvi's (1938 b) variation area of F 1 and F 2 with the means for the same formants obtained in the present study

It is found that, in relation to Sovijarvi's variation areas, the F 1 means of the back vowels of the laryngectomees are located as follows *u*, with the narrowest variation range, at its very bottom, and o and *a* in the central portions Of the front vowels, *a* and *y* are in the lower half, *e* and *o* in the upper half of the variation area, and *i* in the central part

The F 2 means for all back vowels are above Sovijarvi's variation area, in the case of front vowels, the mean for o is the only one taking so high a position, the others being in the upper part of the variation area

The mean frequency range obtained in this study for F 1 and F 2 were also compared with Wiik's frequency data for the corresponding Finnish vowel formants the former was 200—900 cps, the latter 600—2600 cps The mean frequency data for F 1 and F 2 in laryngectomees exceeded not the measured frequency extent The mean frequency measures in laryngectomees — by nature higher than in the controls — moved either farther from or closer to the limits stated, the minimum or maximum limit, according to the designation used (p 20)

The third formant

According to the tabulated data, F 3 of *u*, *o* and *a* is chiefly dependent on the parts in front of the tongue constriction (Fant 1960) F 3 is of secondary importance in the back vowels since it plays no part in the intelligibility of speech However, F 3 was recognizable in all of them, and as in the case of F 1 and F 2, the mean frequency data exceeded those of the controls F 3 of the front vowels on the other hand, played a prominent role their intelligibility is largely dependent on this formant In the laryngectomized individuals F 3 of *i* reached the highest mean frequency level 500 cps above control level while the corresponding value for *e* was 478 cps In the case of *e* the dependency is more equally divided on all sections of the vocal tract F 3 of *i* is chiefly dependent on the parts in front of the tongue constriction (Fant 1960) It thus seems obvious that the altered conditions in the hypopharynx influence about equally the F 3 of *e* and that of *i* The results obtained for the other front vowels showed differences from the control values decreasing in the order *y*, *o*, *a*

The fourth formant

F 4 also showed a mean frequency (320—670 cps) higher than in the control group this formant was only rarely identifiable It is probable that the associated noise in some cases obscured the formant of weakest intensity Because noise usually occurs at the higher frequencies, viz above F 4 it is evident that the laryngeal site of origin of F 4 is the decisive factor in this regard However, the fact that it was possible to determine F 4 a few times shows that under certain conditions a functional cavity — a substitute for the »vestibule of the larynx» — forms above the pseudoglottis In the presence of a normal vocal tract the back cavities have greater influence on F 4 of *u*, *o* and *i*, while the cavity in front of the tongue constriction has an appreciable effect on *a* and *e* (Fant 1960) Since F 4 could be recognized in 15 laryngectomees for none of the vowels and in none of them for all vowels there is every likelihood that, as F 4 originates in the vestibule of the larynx,

the cavity system in front of the tongue constriction is a factor of little significance in the F 4 of some vowels It has been shown by cineradiographic studies that in poor speakers with a bubbling, mucous voice the distance from base of tongue to posterior pharyngeal wall is long (Kirchner), and exactly in these persons, it seems, F 4 is recognizable Sovijarvi stated in 1938 (b) The to some extent definite formant area (K_1) in the vowel spectra concerned is the one which I should like to describe as originating in the upper larynx Its frequency range is 2950—3680 cps, mean 3390 cps The control mean obtained in the present study for F 4 ($= K_1$), 3270 cps is somewhat lower than Sovijarvi's and Wiik reports the corresponding value as 3280 cps Comparison of these figures with the mean F 4 for laryngectomees, 3730 cps, shows that the difference, 460 cps, is greater than in the case of any other variable vowel formant, or of any single vowel for that matter, whether anterior or posterior It is thus found that the anatomic-functional changes due to laryngectomy has had the most influence on the fourth variable vowel formant, having a hypopharyngeal-laryngeal origin

Statistical consideration of formant averages

The formant means obtained were compared with the control means using the statistical probability test of Wilcoxon (p 28), the random variation being significant at the level 0 05

All the other vowels except *u*, *o* and *e* were found to differ significantly as regards F 1 F 2 showed a significant difference in the case of all vowels, whereas the results *for* F 3 *were* evenly distributed in such a way that only one half of the vowels, the front vowels *e*, *i*, *y* and *o*, showed a significant difference

For a clearer description, the above may be summarized by tabulating the vowels showing a statistical difference at the above mentioned level of the random variation, in order according to the formant concerned

F 1			*a*	*a*		*i*	*y*	*o*
F 2	*u*	*o*	*a*	*a*	*e*	*i*	*y*	*o*
F 3					*e*	*i*	*y*	*o*

The result indicates that F 2 is the only formant differing statistically from the control value regardless of the vowel concerned No anatomic-physiological basis was found for the fact that the F 1 *values of exactly u*, o and e failed to show a statistically significant difference It is supposed, however, that since no surgical alteration has been produced in the oral cavity, the vocal [illegible] vowels were in question

The F 3 of none of the three back vowels differed significantly *from* the control values From the point of view of auditory observation F 3 is of

no importance for the vowels and is also of weak intensity The situation is reserved in the front vowels, in which F 3 is necessary for greater clarity of auditory observation, *a* and o being borderline cases, as stated above (Sovijarvi 1955) As a matter of fact *a* here showed no significant difference

Diphthongs

The diphthongs during phonation change in acoustic pattern according to changes in the position of the tongue and lips, and a glide therefore occurs in their formants as required by the situation in each case Each of the diphthongs produces a distinctive pattern composed of the first vowel position from which the glide starts, the glide, and the second vowel position at which the glide terminates (Potter et al 1947) Finnish vowel harmony presupposes that one and the same syllable contains either only back or only front vowels, so any vowel combination requiring a remarkably great glide is impossible The front vowels e and i can be combined also with back vowels and it is exactly in these combinations that the greatest formant transitions are observed

A formant glide, whether ascending or descending, caused the laryngectomees no difficulties, mainly for the reason that we are here concerned with a so-called genio-lingual articulation, which is not directly influenced by laryngectomy Altered formant values, however, may cause even marked changes in the acoustic identification of sounds by the ear This is so, for example, when a back vowel, whose acoustic identification depends on F 1 and F 2, either precedes or follows a front vowel If F 1 of the back vowel has risen considerably, and no equally great change has taken place in the formants of the front vowel (identification dependent also on F 3), then the diphthong has become more difficult to recognize on the basis of auditory observation alone Examples of this are the diphthongs *ui* and *oi* F 1 of *u*, being of higher frequency than usual, here causes the *u* to be perceived by the ear as an o The same appears in the diphthongs ou and uo, which may be difficult to distinguish from the geminate o as the formants glide almost linearly from one vowel to the other In the case of front vowels, the diphthongs become more readily recognizable as the presence of several formants is required for acoustic identification, the variation of one formant in one direction or the other cannot affect the acoustic result

Mutual intensity variation of formants

The intensity registration area of the Sonagraph being limited to 35 dB, it was possible, from the combined decibel frequency scales of the sections, to measure only the relative formant intensities When the mutual, average dB differences for the lowest three formants of each of the vowels were determined, having regard also to the difference in amplitude between F 1 and F 3,

the result was definitely consistent with and related to the respective vowel formant frequencies This was so in spite of the fact that formant intensity in laryngectomees appears highly sporadic, F 2 and even F 3 sometimes reaches the level of F 1

F 2 may be regarded as the one formant which is characteristic of formant variation because of its central position, and expressing as it does the position of the ridge of the tongue in relation to the palate, its intensity decreases with a rise in frequency in the case of back vowels, but increa...

Consonants

A classification based on sound components, of the con... Finnish was presented in Chapter III It was found that ... are characteristic of vowels they play an important p... identifiability of certain consonants too The concepts ... noise consonant, and noise formant consonant emphasiz... only those sound components should be taken into accou... influence the acoustic identifiability of a sound (Sovijarv... tion of the subject, the different consonants will not he... influenced by *a*, *u* and *i*

Vowel-like sounds *v*, *j*, *h*

The initial labio-dental *v* was difficult for the laryn... because of the gradual increase of intensity it frequ... pronounced or fuses with the next vowel without the fo... of semivowels The medial *v*, which as a semivowel rese... appreciable difficulty

The dorso-palatal *j* already presupposes such great a... successfully made even in the initial position, F 1 and ... transition typical of semivowels to the level required ... vowel. Likewise the medial *j* with its formant glide c... normal voice causes no difficulty

The voiced *h*, which — as a laryngeal semivowel — r... rima glottidis is a case apart in laryngectomees In the ... glottidis the oesophageal speaker is found to substitute a ... in which case the formants of the adjacent vowels conti... quency levels in spite of the pause it is also possible th... by a tracheostoma murmur which occasionally resembles ... stop-sound type In good circumstances of phonation ... the anatomic defects an *h* may sometimes be made ... open pseudoglottis preceding chink, which has almo... the normal sound F 1 and F 2 of the adjacent vowels ... without changes in frequency level but being of weak...

spectrum In the laryngectomees as well as in the control persons, a part of the formant noise of *h* comes from the palatal area

The semivowels are always of weaker intensity than the adjoining vowels, both in laryngectomees and in the presence of a normal vocal tract The intensity of *v* and *h* decreased less in laryngectomees than in the control group Subglottic noise here seems to have played a part in levelling the difference Seeing that, in the case of *j*, the reverse is true, it is probable that the required dorso-palatal tongue movement arresting the oesophageal pressure is so powerful as to cause intensity to decrease below the normal value

Liquids *l*, *r*

The apico-postdental lateral *l* and the apico-alveolar tremulant *r*, which is a noise formant consonant, have almost the same formant energy concentration areas The observable spectrographic differences between *r* and *l* are the lower frequency F 3 and generally also the lower F 2 of *r* as compared to *l* (Fant 1959)

The initial *l* is usually perceived by the ear as an explosive noise of stop type (e g *t* or *p*) This as it were holds back the pseudoglottic explosion, following which the acoustic pattern is found to have become indistinct in that the energy is now distributed without clear boundaries of concentration even up to the highest frequencies, without the result being influenced by vowel colouring

The medial *l* is phonated under more favourable conditions, because pseudoglottic vibration has already attained a level rhythm The most characteristic formant area of *l* is the whole range 2000—3200 cps, formant of the buccal cavity, i e of the lateral passages of l-sounds (Sovijarvi 1962) The corresponding results for the laryngectomized individuals were within this range, the upper limit of the i-coloured *l*, which is difficult to define even in fairly noise-free performances, could be as high as 3200—3800 cps In the geminate *l*, where duration adds to the distinctness of the acoustic pattern, the characteristic formant area had a fairly constant lower boundary, 2400 cps, while the upper rose to about 3300 cps

The tremulant *r* contains at least two flaps of the tongue tip and the noise components of the alveolar groove and of the incisors, which give it the character of a noise consonant

Initial position made also the *r* difficult to say there was only one noticeable apico-palatal movement and the acoustic pattern was incomplete Indeed it is only the word as a whole that makes it possible to identify such a noise resembling acoustically a sudden subglottic explosion as an initial *r*

The medial, 3—4 flap *r* is fairly complete compared with the initial one and it is distinct on auditory observation in spite of the slow movement of the tongue during *r* The acoustic pattern is further clarified in the double *r*, where the apicoalveolar flaps (on an average six), articulated at a uniform

rate, are most favourable from the point of view of auditory observation The low-intensity alveolar ridge noise proved difficult to define, but since it was obscured by and resembled the noise from the tracheostoma-pseudoglottis, its absence could not be determined either, for instance by auditory observation

Intensity variation is entirely different in *l* and *r* because of their different nature During *l* intensity decreases obliquely about 10 dB from the preceding level, or about one third more than in the control group The intensity of the geminate *l* falls by about the same extent, 8—10 dB, but then remains at an almost horizontal level After *l* intensity no longer comes up to the previous level but is about 3—5 dB below it

In the tremulant *r*, intensity fluctuation is fairly extensive, 7—12 dB, counted from the flap during which intensity reaches its maximum This is essentially influenced by the interval between flaps as this is prolonged, the difference in intensity increases Moreover it should be noted that the maxima for *r* decline about 10 dB from the level of the preceding vowel In the geminate *r* the same decline is found, but the range of variation from minimum to maximum intensity of flaps is 5 dB The result is the same as in the control group, where *r*, irrespective of its position, retained a range of intensity variation of about 5 dB, and also its total intensity, which was unaffected by the duration of the sounds

Nasal sounds *m*, *n*, *η*

Like the semivowels and the laterals, the nasals are most reminiscent of vowels and so are easy to make for oesophageal speakers, especially as the formants of the lower, middle and upper nasal passages, respectively, which are the typical formants of the nasals, are not directly connected with the hypopharynx-oesophagus

The formant transition playing a part in the acoustic identifiability of the nasals was easy for the laryngectomees The pharyngeal formant, similarly as in the back vowels, reached a higher mean than in the controls, and the same applies to the epipharyngeal formant (F 2) The energy concentration areas of the above three nasal formants could not be identified, but it was possible to determine two isolated concentration areas extending over a broader range

A feature distinguishing the nasals — the anti resonance developing in the oral cavity — which causes disappearance of nasopharyngeal vibration at certain frequencies is present in laryngectomees though it tends to be obscured by noise The sound *η*, where the altered hypopharyngeal conditions are most strongly felt, shows under good conditions of phonation more clearly than *m* and *n* that owing to diminished cavity size, the damping area has risen and has also become narrowed partly as a result of the width of the nasal resonance area

A fall of 10—12 dB in intensity compared with the adjacent sounds was found in all of the nasals, and the control tests yielded a similar result In geminates the decrease in intensity is less abrupt, so the intensity maximum is not attained until at the end of the nasal sound

Fricative sounds *h, s*

In dealing with the semivowels the voiced *h* was already considered it is one of the two Finnish *h*-variants and occurs between voiced sounds The voiceless *h* occurring in other positions, for example initially, naturally also requires a half-open rima glottidis, and so is difficult for anatomical reasons

The unvoiced *h* of course resembles the voiced *h*, but in the initial position, to which this study is confined, it is very difficult for laryngectomees This is apparent even from the fact that, more often than the voiced *h*, its voiceless equivalent fails to be pronounced or tends unconsciously to be replaced by explosive noise of stop sound type However, at times — evidently only in extremely good conditions of phonation — a sound is produced with the typical *h* formants required by the following vowel, and this raises the question whether this also is indeed an *h* followed by a vowel of weak intensity The *h* perception on auditory observation is further emphasized by the pause which always precedes the next vowel

The medio-alveolar voiceless *s*, being a pure noise consonant and resembling the noise from the tracheostoma-pseudoglottis was generally successfully articulated by the laryngectomees from the acoustic point of view, despite the fact that the characteristic noise concentration areas are not recognizable in the single *s* This bears no relationship to the localization of *s* during phonation Only in the double *s*, whose longer duration reduces other noise and thus creates more favourable conditions, the characteristic components were about 1000 cps higher than the corresponding control value

The initial *h* is of 10—15 dB weaker intensity than the following vowel The explosive noise of stop sound type, when substituted for *h*, mostly is of equal intensity as the vowel that follows

The *s* usually has the same intensity level as the following vowel The noise component may sometimes in laryngectomees be so strong as to cause some increase in intensity during *s*, about 5 dB above the level of the next sound Before the *s* as the tongue assumes a medio-alveolar position, intensity falls about 10 dB but, after the transition phase, is restored to the initial level or even beyond it, as stated in the foregoing In the geminate *s* this pre-*s* pause is lacking intensity falls 10 dB from the level of the preceding sound and remains unchanged up to the following sound

Plosives p, t, *k*, *d*

Analysis of the voiceless plosives even in the normal voice entails certain difficulties When proceeding to analyse the explosive noise associated with the stop sounds made by laryngectomees, this task is found to be well-nigh

impossible as this sound is extremely rapid and evidently requires that both oesophageal pressure and its speed of explosion are maximal, a column appears in the sonagram where energy is almost equally distributed over the range 80—8000 cps Thus it is impossible even roughly to define the noise concentration areas, their number and their location In Finnish the tenuis plosives are associated with *no aspiration, which would prolong the explosive* noise — otherwise of very brief duration — and therefore the tenuis plosives for example between vowels are identified by directing auditory observation to the first part of the succeeding vowel or the terminal part of the preceding vowel, besides to the explosive noise (Sovijarvi 1961) On this basis we can understand that the auditory observation group was on the whole able without difficulty to recognize the plosives in post-laryngectomy speech, notwithstanding their acoustic weakness Obviously *p* was the easiest, *t* followed next, and *k* came last because it is of velar origin and is most likely to become mixed with noise The position of the plosive was of no consequence in this respect

The only voiced plosive, *d*, acoustically resembles *t*, and many laryngectomees in fact substituted the latter for the former, for which their dialect may have been partly responsible The voiced portion of *d* proved of shorter duration and of higher frequency than in the controls As in the case of the other plosives, the explosive noise in *d* contains such an amount of evenly distributed energy that it could not be analysed in greater detail For the purpose of auditory observation *d*, evidently for the reasons outlined above, proved very satisfactory though often t-like

The intensity in plosives is invariably maximal, which understandably bears a relationship to the rapid articulation

The pseudoglottis

Cineradiographic examination showed that the pseudoglottis — defined as the most cranial narrowing in the lumen of the oesophagus or of the pharynx over which the contrast medium is seen vibrating (Damste 1958) — was located in 5 of the 6 laryngectomees thus studied at the level of the V—VI cervical vertebrae, only one pseudoglottis, with higher location, differed definitely in this regard It has been found in several studies that exactly this level (C V—VI) is the most common location of the pseudoglottis in accomplished speakers (Hoople & Brewer, Vandor, Mockel & Schlosshauer, van den Berg, Robe et al Motta et al., Černoch & Žobril, Kirchner et al)

As the location and shape of the pseudoglottis is determined by the cricopharyngeus the greatest care should be taken to conserve this muscle at operation (e g Negus, Tarneaud, Levin 1952, Hodson & Oswald, Sercer, Damsté 1958)

Four of the pseudoglottises studied were of similar appearance, club-shaped the »shaft» being thinner than the head The best pseudoglottis

has been described as being of this shape In poor speakers the pseudoglottis is often only a low bulge in the dorsal oesophageal wall or is otherwise of more irregular shape (Mockel and Schlosshauer, Lindsay, Vandor, Damste 1958, Levin 1952, 1962)

There are cases, however, where a pseudoglottis found roentgenographically to be of poor shape, may prove perfect from the point of view of auditory observation, and this latter opinion may even be corroborated by the sonagram, as in one of the cases in this investigation Indeed it appears evident that a factor of essential importance in this respect is the dorsoventral distance at the site of the pseudoglottis the smaller it is, the greater the extent to which the so called Bernoulli effect will show up According to van den Berg, »the walls are sucked towards each other by the negative pressure in the pseudoglottis and this effect increases the effective stiffness of the muscular structures, which then vibrate at a higher frequency, as their mass remains the same

In good speakers a distinct sagittal fold has also often been described in the ventral oesophageal wall (Mockel & Schlosshauer, Vandor, Damste 1958, Levin 1962, Fumeaux), which favourably completes the air closure produced by the pseudoglottis Such a ventrally situated sagittal fold was also present with varying distinctness in the four similar pseudoglottises referred to above, but was absent in two other laryngectomees examined roentgenologically

The fundamental frequency is definitely related to the shape and location of the pseudoglottis, though it is greatly influenced also by incidental factors, such as mucus and variations in oesophageal pressure, etc It is possible that the pseudoglottis, depending upon the conditions in each case, develops sometimes more successfully, sometimes less so, and it seems that, from the point of view of fundamental frequency, the location of the pseudoglottis is of primary importance and its shape takes second place

SUMMARY

It was the purpose of the present study to determine

1 The fundamental pitch of oesophageal speech and the factors influencing it

2 The vowel formant structure of oesophageal speech and formant intensities as compared with each other

3 The acoustic qualities of consonants in oesophageal speech

4 The site and shape of the pseudoglottis and the part played by it in the fundamental pitch of oesophageal speech

The series consisted of 27 men (average age 51 years 4 months) laryngectomized for carcinoma of the larynx who had become accomplished speakers and in whom oesophageal voice development could be considered terminated They were subjected to spectrographic sound quality analysis of the voice using the Sonagraph in an attempt to determine the physical properties of the oesophageal voice as set out under points 1—3

To bring out each of the phonetic factors of Finnish speech the test subjects were asked to say all eight vowels separately and in addition the 63 test words These latter had been chosen in such a way that the three most important vowels two back vowels the open unrounded *a* and the close rounded *u* as well as the close unrounded front vowel *i* occurred on each side of those 14 single and 14 double consonants which are included in the present investigation Thus it was possible to make observations concerning the consonant variants having the colour of *a* *u* and *i* When the test words permitted it attention was paid also to the acoustic pattern of initial consonants The 16 diphthongs occurring in Finnish speech 13 descending and 3 ascending ones as well as the vowel combinations *iu* and *ey* to be included among the diphthongs were also analysed

For control purposes 25 men were selected who equalled the laryngectomees in age and whose voices were of a quality well corresponding to the loss of laryngeal tones in the laryngectomees.

Further six laryngectomees chosen at random were subjected to a cineradiographic examination to elucidate point 4 they said the most important vowels (*a* *u* *i*) both with and without opaque medium ($Ba SO_4$)

The following results were obtained

1 The essential factor in the fundamental pitch of oesophageal speech is the fundamental frequency which was found to average 50 4 cps in 18 subjects In the others this was impossible to determine because of unfavourable noise factors Another point worth noticing is in fact the great number

of noises associated with the low fundamental frequency, the swallowing sound from intake of air, the noise from the tracheostoma, and accumulation of mucus in the hypopharynx may all, together or separately, have very undesirable effects In the last of these cases, the air utilized in speaking must force its way through layers of secretion of varying thickness, and this results in a noise rather than in a resonant voice

Fundamental frequency was found to vary in single vowels from 32 to 72 cps, and the mean for different laryngectomees from 36 7 to 60 5 cps The mean frequency data for the various vowels showed no statistically significant differences It is almost impossible for a laryngectomee to change fundamental pitch under voluntary control in either direction This occurred unconsciously average variation in different individuals irrespective of the fundamental frequency was 14 7 cps, which corresponds to 3—4 tones, as against 2 5 tones in the controls

2 All four vowel formants showed higher mean frequencies than the control cases, in spite of the fact that fundamental frequency in the laryngectomees was c one octave below the control value In the case of the lowest three formants a comparison was made with the control values and a statistically significant difference found as follows F 1, all vowels except *u*, *o* and *e*, F 2, all vowels, F 3, the front vowels *e*, *ı*, *y*, *o*

Notwithstanding its laryngeal origin, F 4 was recognizable a few times and had a mean frequency about 460 cps higher than the control values regardless of the vowel concerned The fact that it was nevertheless possible occasionally to demonstrate the fourth formant shows that a functional cavity substituting for the vestibule of the larynx sometimes forms in the hypopharynx, above the pseudoglottis.

It is seen that the intensity of the back vowels was generally greater than that of the front vowels, also in the control group, and further that the intensity of the back vowels in laryngectomees was greater than in the controls while the opposite is true of the front vowels

F 2 is to be considered the formant characteristic of intensity variation, because of its central position and as it reflects the tongue-ridge position in relation to the palate, it reduces intensity with increasing frequency in the case of back vowels, whereas intensity increases correspondingly in the front vowels

Thanks to their genio-lingual articulation, which is not directly affected by larygectomy the diphthongs were well pronounced the formant glide was successful in both ascending and descending direction

3 The consonants of standard Finnish fall into five separate categories on the basis of enunciation

a) The vowel-like sounds *v*, *j*, *h*, being semivowels, usually were well pronounced A special case, however, is the voiced *h* which, since it is of laryngeal origin requires a half-open glottic chink In its absence, oesoph-

ageal speakers are found to substitute a pause for this sound or the *h* is replaced by a pseudoglottic murmur which may occasionally resemble an explosion of stop-sound type

b) Liquids *l*, *r* Both the lateral *l* and the tremulant *r* caused certain difficulties when in initial position in both cases the acoustic pattern was indistinct in that energy was distributed without definite concentration areas, the result was not influenced by vowel-colouring Recognition of the sound, in fact, is only possible from the word as a whole When these sounds are in medial position, the conditions of phonation are already much better, since also pseudoglottic vibration has reached a level rhythm

c) The nasal sounds *m*, *n* and *ŋ*, resembling vowels, usually were well articulated from the acoustic point of view, even though the formants of the lower, middle and upper nasal passages, respectively, typical of the nasals, could only be identified as two separate energy concentration areas, which were broader than in the control group, however The formant transition required for acoustic identification of the nasals was perfect and appeared clearly, the anti-resonance caused by the oral cavity was also recognizable, and as a result of it nasopharyngeal vibration disappeared at certain frequencies the distinctness of this phenomenon suffered to some extent from being obscured by noises

d) Fricative sounds *h*, *s* The same difficulties were apparent in the fricative *h* as in its voiced equivalent The difficulty of making this sound is greater still when it is initial, and this is indicated also by the fact that, more often than the voiced *h*, the voiceless *h* remained unpronounced or tended to be substituted by an explosion of stop-sound type

The voiceless sibilant *s* resembling the noise from the tracheostoma-subglottis, was satisfactory from the point of view of auditory observation in spite of the fact that characteristic noise concentration areas were not recognizable in the single *s* In the geminate *s* where conditions become more favourable because temporal prolongation reduces other noise, the characteristic components were found

e) The plosives *p*, *t*, *k* and *d* are the most difficult consonants for laryngectomees they are temporally very rapid and require a maximal oesophageal pressure and a great speed of explosion and thus the sonagram shows a column where energy is of almost equal strength throughout the entire area of analysis The acoustic result is improved by observation being directed also to the initial part of the following vowel or to the terminal part of the preceding vowel

4 Cineradiographic examination was performed on 6 laryngectomees in 5 of them the pseudoglottis was found at the level of C V—VI and in one at C IV—V Of the pseudoglottises four situated at the level C V—VI were almost similar, club-shaped with the »shaft» narrower than the head The fifth pseudoglottis at the same level was more poorly shaped having the appearance of a low bulge in the dorsal oesophageal wall In all these

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THE EFFERENT VESTIBULAR SYSTEM

Electrophysiological Research

BY

O. SALA

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From the Oto-rhino-laryngologic Clinic, University of Padua (Italy)
(Head: Prof. M. Arslan)

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CONTENTS

pheral receptors can modify the functional state of the r s which in its turn is capable of modulating the activity of the receptors themselves by means of the centrifugal system of efferent fibers (efferent gamma fibers) This mechanism is of basic importance for the understanding of the muscular tone as well as the automatic and voluntary motory activity

GRANIT (1955 *c*) has also demonstrated a similar mechanism at the level of the *etinal receptors* He produced bioelectric retinal activity by means of low intensity light stimuli Stimulation of the mesencephalic r s (with repetitive stimuli of tetatinizing frequency at the intensity of 5 10 V) caused a distinct reduction of the bioelectric activity produced by the light stimuli on the retinal receptors and it was then followed by a period of distinct facilitation of the discharge itself

The above phenomena can be explained according to GRANIT only by postulating that the electrical stimulation of the mesencephalon produced a specific activation of the r s of the brain stem which in turn was capable of modulating the retinal activity through a system of specific efferent fibers identified as the bundle of Cajal These experiments constituted the direct demonstration of this efferent system whose existence had been questioned by anatomical experiments (POLYAK, 1941)

These results were entirely confirmed and integrated by DODT (1956) and other AA and recently by FERNANDEZ *et al* (1962) FUSTER & DOCTOR (1962) JANE *et al* (1962) etc

When interpreting the work done on the retinal receptors GRANIT suggested the hypothesis of an analogous autoregulatory system entering into play for other receptors as well

Centrifugal fibers projecting to the *olfactory bulb* were described by CAJAL (1909 1911) ALLISON (1953) and CRAGG (1962) originating from the olfactory tubercle prepyriform cortex and anterior commissure

The low frequency stimulation of intralaminar thalamic nuclei causes recruiting waves in the olfactory bulb (ARDUINI & MORUZZI 1953) high frequency electrical stimulation of basal rhinencephalic structures suppresses the olfactorily evoked activity (KERR & HAGBARTH 1955) electrical stimulation or removal of the prepyriform cortex modifies the adaptation of the olfactory stimulation (ANTONELLI 1960 1962) In the olfactory bulb « internalized patterns » in the blocking of the olfactory impulses were described (ORREGO 1962)

LAVIN *et al* (1959) demonstrated that « during arousal and alertness activation is produced in some intrinsic elements of the olfactory bulb by centrifugal influences from the mesencephalic tegmentum of the brain stem » and that « arousal discharge » in th[illegible] olfactory bulb appeared together with the desynchronization of the electr[illegible] the septal area It is worth mentioning that also non olfactory [illegible] late the olfactory relays activity (ADEY *et al* 1962

GALAMBOS (1956) was able to demonstrate that *the efferent cochlear system* of which the olivo-cochlear bundle of RASMUSSEN constitutes the most peripheral part has the function of regulating the complex bioelectrical *activity of the cochlea*. In experimental preparations used by this A. bioelectrical activity of the cochlear nerve induced by a click was reduced or abolished by simultaneous electrical stimulation of different intensities at the level of the decussation of the olivo-cochlear fascicle of Rasmussen. The section of this fascicle resulted in disappearance of the above phenomena.

These results were later confirmed by FEX (1959, 1962 *b*), PFALTZ (1962 *a*, 1962 *b*, 1962 *c*) and other AA. Among these researches it is worth mentioning the following ones because of their pertinance to this paper.

FEX (1959) besides recording the inhibitory effect on the action potential of the cochlear nerve, was also able to record a simultaneous increase in the microphonic cochlear potentials. FEX (1962 *a*, 1962 *b*) in later researches on this subject could directly record the electrical activity of fibers in Rasmussen's fascicle, and defined the physiological properties in relation to the auditory function.

ANTONELLI (1963) studied the modifications in the thalamo-cortical transmission of the auditory impulses during different states of activity of the central nervous system (in spontaneous wakefulness and sleep, during stimulation of the reticular formation and after its electrocoagulation, after the suction of the A. I. cortical area, etc.).

DESMEDT (1960) and DESMEDT & MECHELSE (1957, 1958, 1959) were then able to demonstrate electrophysiologically the existence of fibers and centrifugal relays of cortical origin (temporo-insular cortex) capable of controlling the activity of Rasmussen's fascicle.

The researches we have briefly summed up allow to conclude that there is actually an aspecific as well as a specific centrifugal control of the extero-intero- and proprioceptive input. This control is performed by aspecific means and particularly by the reticular substance of the brain stem.

As to the olfactory and auditive functions, it was also demonstrated electro-*physiologically that there are specific polysynaptic systems functionally rela*ted to well defined cortical areas.

Therefore the centrifugal fibers reaching the receptors are to be considered the terminal part, more peripheral and anatomically more easily demonstrable, of these specific efferent systems.

* * *

Recent hystological (PETROFF, 1955; WERSALL, 1956, 1960; ENGSTROM, 1958; RASMUSSEN & GACEK, 1958; ENGSTROM & WERSALL, 1958; CARPENTER, BARD & ALLING, 1959; GACEK, 1960; CARPENTER, 1960; LUBATO & TAIDELLI, 1961) and histochemical researches (DOHLMAN, FARKASHIDY & SALONNA, 1958; IRELAND & FARKASHIDY, 1961; ROSSI & CORTESINA, 1962, 1963; HILDING & WERSALL, 1962;

ROSSI 1964) demonstrated *centrifugal vestibular efferent fibers* in their terminal part at the level of the brain stem and of the vestibular receptors

ROSSI & CORTESINA's research work (1962) on guinea-pig is to be mentioned here since it brought to the discovery of a complex efferent vestibular system composed of specific nuclei and bundles

The demonstration of the physiological properties of the efferent vestibular system was carried out by SALA (1962, 1963, 1964) in the cat with the aid of an electrophysiological procedure

SCHMIDT (1963) later gave the direct demonstration of an efferent activity from the free ends detached from the ampullae, sacculus, utriculus and lagena in the frog which could be evoked by several types of stimuli (rotation and tilting movements vibratory and auditory stimuli)

GLEISNER & HENRIKSSON (1964) confirmed the existence of an efferent activity in the vestibular nerve of the frog from the proximal end of the cut nerve and from the intact lateral ampullar nerve, these AA are inclined to interpret it as a prevalently inhibitory function of the efferent vestibular system

RESEARCH PURPOSE

Experiments were undertaken with the aim of demonstrating the modifications induced by the stimulation of the efferent vestibular system (e.v.s) in the afferent vestibular activity The afferent activity was recorded at the level of the vestibular nerve (I experiment series) as well as at the level of the vestibular receptors (II experiment series) It was thus possible to study what the *effect of the e.v.s* is both *on A) the action potentials of the vestibular nerve*, and *on B) the excitatory state of the vestibular receptors themselves* A possible presence of a feed back loop mediated by the e.v.s was also investigated

I) EFFERENT INFLUENCE ON VESTIBULAR NERVE ACTIVITY

Technique and Procedures

All experiments were performed on normal adult cats (20 animal weighing from 2 to 4 Kg) Ether anesthesia was used during the early stage of the experiment tracheotomy was performed for tracheal cannulation, both bullas were visualized by dissection of the muscles of the head and neck and opened to put in a cotton plug imbibed with physiologic solution The occipital bone was then removed and the cerebellum suctioned out to reveal the floor of the IV ventricle and the vestibular nerves coming out from the internal auditory mea

tus. The recording of the electrical discharge of the vestibular nerve was made in the waking animals immobilized by curarization (2 mg/Kg) and supplied with controlled respiration. All the exposed nervous structures were protected by paraffin oil maintained at body temperature. The head was fixed in the Horsley-Clarke apparatus; the steel electrode, thinned down to 30–40 micron by means of electrolysis and insulated except at the tip, was then placed upon the vestibular nerve and controlled by a manipulator graduated in micron steps. The indifferent electrode, which was represented by a screw, was fixed in the frontal bone. The impedance of the electrodes was in the order of 10 Kω and therefore it was not necessary to use the cathode follower.

The electrodes were connected with a model 122 Tektronik A. C. preamplifier and with an E.T.C. model K 21 A cathode ray oscilloscope supplied with camera for recording in bromide paper.

The cotton plugs placed in the bullas were connected with a galvanic current generator in order to stimulate the labyrinth by means of galvanic current at different values varying from 0 to 0.5 mA after LOEWENSTEIN's technique (1955).

The contralateral nuclear region was stimulated by means both of unipolar (300 micron tip diameter) and bipolar concentric (external = 0.2 mm, internal = 0.15 mm) electrodes placed in the floor of the IV ventricle near the Deiters nucleus. Maps of the brain stem of the cat were used with a view to identify the exact position of the tips of the electrodes through the stereotaxis apparatus.

Electric square wave stimuli were used whose frequency, pulse duration and voltage output could be modified at will. The square waves were generated by a completely transistorized apparatus (CALPUCCINI & DEBIASI, 1961); the duration of each stimulus was from 0.1 to 1 msec and the magnitude from 0.5 to 4 Volt. The artifacts were reduced by means of a stimulus isolation unit.

The site of the stimulated points was then obtained by the input of a galvanic current of 0.15 mA for 15"-20"; the positive pole was connected with the stimulating electrode. The iron ions that were thus released were later coloured histologically by the Prussian blue method. In some animals the stimulated points could be localized also by electrolitic lesion.

Results

Our experiments have further confirmed that the vestibular nerve is the site of spontaneous electrical activity of a median frequency of 5-15 impulses/sec (ASHCROFT & HALLPIKE 1934; ROSS 1935, 1936; LOEWENSTEIN & SAND 1936; GERNANDT 1949; LEDOUX 1958).

Cathodic galvanic stimulation of the labyrinth using Loewenstein's technique produced a distinct increase in the frequency of the resting potentials, whereas anodic galvanic stimulation reduced the resting potentials to the point of total inhibition.

These responses to galvanic stimulation of fibers whose activity was recorded established the fact that the recording electrode was placed exactly on the vestibular nerve

The form of the resting potentials varied in each preparation, at times the wave was monophasic and positive, sometimes negative and biphasic, followed by a positive wave of equal voltage The varied form of the potentials, as is known is due to the variation in the position of the point of the recording electrode with respect to the fiber or group of fibers whose activity has been recorded

Stimulation with bipolar electrodes of the floor of the IV ventricle was performed in various parts of the contralateral vestibular area, only the stimulation of the contralateral vestibular area at the level of Deiters nucleus, produced in the vestibular nerve spikes equal to those of the resting state

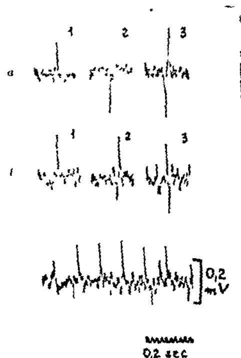


Fig 1 Patterns of spontaneous and evoked potentials in left vestibular nerve Curarized cat

a Spontaneous action potentials of the vestibular nerve

1 Positive monophasic spike
2 Negative monophasic spike
3 Diphasic spike

b Evoked potentials, obtained from stimulation with single electric shocks applied to the right Deiters nucleus (artifacts downward)

1 Positive monophasic spike, 32 msec after stimulation
2 Diphasic spike, with a small initial negative phase, 26 msec after stimulation
3 Diphasic spike, with the same amplitude of positive and negative phases 32 msec after stimulation

c Repeated stimulation (12 cps) shows repeated bursts in unit from vestibular nerve, 32 msec after stimulation

In *fig 1* one can observe in tracing *b* 1 that electrical stimulation (indicated by artefacts was followed after a latency of 32 msec, by a monophasic positive potential of the same form as the resting potential shown in *a* 1 In tracing *b* 2 the positive wave is preceded by a small negative wave whereas in tracing *b* 3 the positive wave is followed by a negative wave The latencies were respectively 26 and 32 msec

In tracing *c* of *fig 1* repetitive stimulation (5 impulses at the frequency of 12 impulses per sec was always followed after a latency of 32 msec) by a monophasic positive wave which demonstrated the constancy of the above phenomena

In tracing *b* of *fig* 2 the results obtained in other preparations are shown In them single stimuli were followed after a latent period of 28 msec by a positive monophasic wave In tracing *c* of the same figure a biphasic resting potentials is followed after a latency of 22 msec by a discharge exactly equal to the preceding one

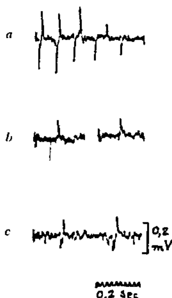


FIG 2 As fig 1 Other preparation

a Spontaneous action potentials of right vestibular nerve Diphasic and monophasic spikes with various amplitude

b Positive monophasic spike 28 msec after single shock applied in the left Deiters nucleus

c Spontaneous (left) and evoked (right) diphasic spikes To be noted the same shape of the two spikes (latency 22 msec)

In some experiments resting potentials of the vestibular nerve underwent a distinct reduction in frequency during tetanic stimulation of the same region of the floor of the IV ventricle (the region surrounding contralateral Deiters nucleus *figs* 3 and 4)

Midline shallow cut performed on the floor of the IV ventricle at the level of the raphe at the depth of approximately 2 mm and extending from the eminentia teres to the obex completely abolishes all observed phenomena at the level of the vestibular nerve following stimulation of the contralateral vestibular area

Discussion

The results of this first series of experiments show that electrical stimulation of the floor of the IV ventricle at the level of Deiters nucleus can cause a variation in the afferent activity of the contralateral vestibular nerve These results allow us to suggest that these modifications of the activity of the contralateral vestibular nerve can only be interpreted as due to stimulation of the efferent vestibular system

We are now trying to find out on which point we have exerted the electrical stimulation of the e.v.s. Anatomic researches do not agree as to the originating point of the efferent vestibular fibers, and particularly as to whether they are crossed (PETROFF, 1955, in the cat and the monkey, CARPENTER *et al.*, 1959, and CARPENTER, 1960, in the cat, as regards the fibers from the fastigial nucleus), or uncrossed (RASMUSSEN & GACEK, 1958, in the cat, GACEK, 1960, in the cat, ROSSI & CORTESINA, 1962, 1963, in the guinea pig).

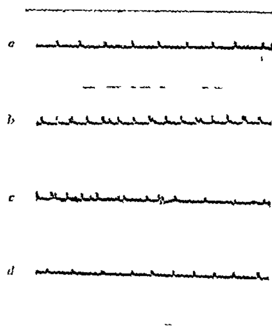


FIG. 3. As figs. 1 & 2. Other preparation. Reduction in frequency of the spontaneous action potentials of the right vestibular nerve during stimulation of the floor of the IV ventricle close by the left Deiters nucleus.

a. Spontaneous action potentials of a single unit of right vestibular nerve.

b & *c.* Repeated stimulation of the floor of the IV ventricle (artifacts upward) evokes a distinct reduction in the frequency of spontaneous potentials of the contralateral vestibular nerve (right nerve).

c & *d.* Spontaneous action potentials after stimulation of the floor of the IV ventricle.

The effects we achieved may be regarded as a direct stimulation of the crossed efferent fibers likely at the level of what is considered their originating site (area of Deiters nucleus, RASMUSSEN & GACEK in the cat). Doubts as to the existence of crossed efferent fibers do not infirm the validity and interpretation of our results, since in any case we must admit that the e.v.s. may have been activated through unknown internuncial neurons.

On the other hand, we have already remarked that the various specific efferent structures found at the level of the brain stem and receptors are but the distal part and therefore the most easily demonstrable one from an anatomic point of view of a system.

The very same conclusions were reached by FEX (1962 *a*) as regards the cochlear efferent system. DESMEDT & MECHELSE (1959) have furthermore demonstrated that this system is a polysynaptic one originating in the temporo-insular cortex (IV auditive area according to DESMEDT & MECHELSE).

On the other hand, in this series of experiments it was not possible to stimulate the e.v.s. ipsilaterally to the vestibular nerve where the action potentials were derived without allowing for an antidromical conduction of the square wave stimulation of the brain stem through the primary afferent vesti-

bular neurons, which was to be excluded completely This stimulation was instead possible, as we will see, in the second series of the experiments

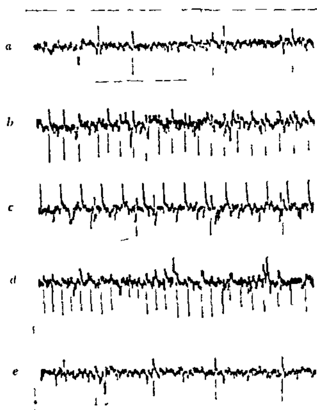


Fig 4 As figs 1 2 & 3 Other preparation

Vestibular potentials, evoked by cathodic polarization of the labyrinth are reduced in frequency during stimulation of the floor of the IV ventricle (region surrounding contralateral Deiters nucleus)

a: Spontaneous action potentials of right vestibular nerve

b Potentials of right vestibular nerve evoked by cathodic polarization of the right labyrinth

c Potentials evoked by cathodic polarization (*b*) underwent a distinct reduction *during* stimulation of the region surrounding contralateral Deiters nucleus (artifacts upward)

d Potentials evoked by cathodic polarization of the labyrinth *after* stimulation of the region surrounding contralateral Deiters nucleus frequency is equal to the preceding one (*b*)

e Spontaneous action potentials of right vestibular nerve frequency is equal to the preceding one (*a*)

We must point out the *different effect* of the *single shock* which resulted constantly in the appearance of an afferent activity of the contralateral vestibular nerve compared with the *tetanic burst* causing constantly an inhibitory effect both on the spontaneous action potentials of the vestibular nerve and when the action potentials were increased in frequency by galvanic stimulation

There are some main objections to this interpretation of our results

The *first objection* is that the potentials recorded at the level of the vestibular nerve are only antidromic discharges travelling along the vestibular nerve following stimulation of the contralateral vestibular area (the important anatomo physiological relations existing between the vestibular nuclei of both sides are well known GERNANDT & THULIN 1952 BRODAL *et al* 1962 etc)

This possibility can be excluded by the long latent period between the stimulation of the floor of the IV ventricle and the appearance of the potentials of the contralateral vestibular nerve If they were antidromic discharges the two phenomena would be almost superimposed On the other hand primary vestibular fibers do not cross the midline (WALBERG *et al* 1958) This reason may also be invoked to exclude the possibility that the derivation at the level of the vestibular nerve was produced by vestibular neurons of the second order that is that this phenomenon may be only a simple internuclear effect

The *second objection* concerns the possibility that modifications of bioelectrical activity of the vestibular nerve are caused not by stimulation of the e v s as much as by a simple diffusion of electric stimulus to vestibular receptors through the nerve tissue of the IV ventricle

This second objection we believe to be invalid for the following reasons *a*) long latency *b*) comparatively moderate intensity of stimuli and small surface area stimulated *c*) disappearance of the above phenomena caused by mid line section of the floor of the IV ventricle (if it were a matter of aspecific diffusion of the stimulus through nerve tissues the stimulus would be conducted over the midline section) *d*) the fact that the stimulation of only certain points of the floor of the IV ventricle is capable of producing the above modifications The least shifting of the stimulating electrodes in the floor of the IV ventricle is sufficient to make these phenomena disappear

The *third objection* concerns the fact that the electric activity of the vestibular nerve is derived not only from the axis cylinders but also from cell bodies scattered throughout the nerve fibers (hypothesis suggested by GERNANDT 1949) In this case the phenomena we observed could be due to interneuronic influence among vestibular fibers of the second order We believe that such a possibility may be excluded by the fact that cell bodies scattered throughout the vestibular nerve belong functionally to Scarpa s ganglion that is they are first order nervous fibers (BRODAL *et al* 1962)

The phenomena we observed can therefore be explained by postulating that stimulation of the floor of the IV ventricle causes an activation of the e v s directly or indirectly In the latter case by stimulation of nerve structures in close anatomic relation with the e v s

B) EFFERENT INFLUENCE ON VESTIBULAR DC RESTING POTENTIALS

The vestibular DC resting potentials (vest DC r p) have been described by TRINCKER & PARTSCH (1957) and by TRINCKER (1959), this A observed that utriculopetal deflection of the cupula of the lateral semicircular canal causes a depolarization of the crista while the utriculofugal deflection causes a hyperpolarization Opposite phenomena were observed in the vertical semicircular canals

Later ELDREDGE *et al* (1961) have substantially confirmed Trincker's results, though the results did not quite agree as to the absolute values of the vest DC r p recorded in different parts of the membranous labyrinth

In our experiments we did not aim at a study of the absolute values of the vest DC r p , the values we reported therefore concern only the modifications in the vest DC r p induced by the thermic stimulation of the labyrinth or by electric stimulation of e v s

In our experiments the vest DC r p at the niche bored at the level of the crus commune were found to be 0 5-1 millivolt relative to a reference point outside the labyrinth

Technique

The experiments of this second series were performed in 25 adult cats weighing between 2-4 kg Under ether anaesthesia, animals were tracheotomized and decerebrated precollicolarly, sometimes also decerebellated after legature of the common carotid arteries, the brain was removed and a cotton plug imbibed with physiological solution was placed in the hollow of the skull The fissured myosis appearing after decerebration showed the integrity of the mesencephalon, an indispensable condition as is known, to the extrinsecation of the nystagmic reflex from labyrinthine stimulation (DE KLEIJN, 19) After removal of the tentorium the part of the cerebellum overlying the left and/or right petrous bone was sucked away

A small niche was then bored by microdrill in the petrous bone under six time magnification, at the level of the crus commune This niche reached the endostium, sometimes also the perylymph We paid attention not to touch the wall of the membranous labyrinth at all

The vest DC r p were recorded with a Hewlett Packard microvoltmeter The variations of the vest DC r p were directly read on the dial of the microvoltmeter Chlorided silver wires were used as electrodes, with a 0 15 mm diameter, insulated except at the tip The active electrode was placed on the small niche at the level of the crus commune, and the indifferent electrode at a short distance upon the skull bone

teral and ipsilateral areas of the Deiters nuclei and region of the raphe between the two Deiters nuclei).

3) **Third procedure.** The electrical stimulation of the e.v.s. was performed as soon as the thermic (warm or cold) stimulation of the recorded labyrinth had caused the maximal modifications of the vest. DC r.p.

This experimental modality allowed us to study the activity of the e.v.s. on a labyrinth under conditions of modified functional activity (depolarization or hyperpolarization) induced by a simultaneous thermic stimulation (respectively warm and cold).

4) **Fourth procedure.** Strychnine sulphate was administered intravenously (0.10 mgr./body Kg.) in order to study its effect during stimulation of the e.v.s. following the technique used by DESMEDT & MECHELSE (1957), DESMEDT (1960), DESMEDT & MONACO (1960) and FEX (1962 *a*) in their experiments on the cochlear efferent system. It is known that these AA. in this way blocked the effect of electrical stimulation of Rasmussen's bundle on cochlear potentials.

Results

1) Modifications induced on vestibular DC resting potentials by thermic « stimulation » of the labyrinth.

The thermic stimulation of a labyrinth constantly causes a *variation in the vest. DC r. p. of this labyrinth.* In particular, the warm thermic stimulation causes a depolarization of the vest. DC r. p., the cold one a hyperpolarization. The change in the vest. DC r. p. was maximally of 300 microvolt. The intensity and duration of these phenomena vary according to the intensity of the thermic stimulus, though there are differences from animal to animal according to the conditions of the experimental preparations.

This allows us to conclude that the potentials generated at the level of the lateral semicircular canal could be recorded even if the recording electrode was placed at the level of the crus commune. In two animals only opposite phenomena were observed, that is the warm thermic stimulation caused a hyperpolarization, the cold one a depolarization. This is likely to be due to the fact that in that case the recording electrode mainly derived the vest. DC r. p. from the vertical semicircular canals.

Along with the modifications of the vest. DC r. p. the thermic stimulation evoked an ocular nystagmus with the fast component directed respectively ipsilaterally under warm thermic stimulation and contralaterally under cold thermic stimulation. The jerks struck in the transversal plane of the orbit.

Generally the duration of the modification of the vest. DC r. p. resulting from the [illegible] stimulation was equal to the duration of the nystagmic reflex. In some [illegible] however the nystagmus lasted longer, that is even after the vest. DC r. p. had returned to normal values. In those cases the nystagmus

would lose its rhythmical character and become ondulatory or showed a preva lence of the slow phase, which suggests that it was an ocular nystagmus due to phenomena of central origin (ARSLAN & SALA 1956 ARSLAN, 1963, etc)

Thermic stimulation of a labyrinth causes the *contemporaneous* appearance of *opposite phenomena* at the level of the *contralateral labyrinth* that is, warm thermic stimulation causes hyperpolarization, the cold one depolarization

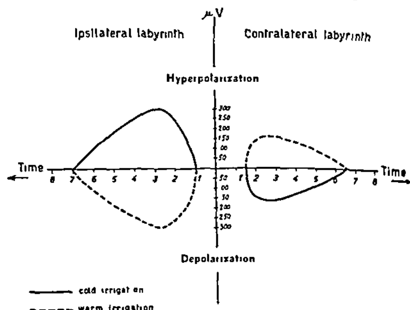


FIG 6 Feedback loop between the two labyrinths
Time indicated in relative units
Cold water irrigation of one ear causes a hyperpolarization of DC resting potentials of lateral labyrinth and *simultaneously* a depolarization of DC resting potentials of the lateral labyrinth
Warm water irrigation of one ear causes a depolarization of the DC resting potentials ipsilateral labyrinth and *simultaneously* a hyperpolarization of DC resting potentials contralateral labyrinth
The modifications of DC resting potentials of the nonstimulated labyrinth longer latency and reach a smaller intensity

The intensity of these variations of the vest DC r p in the labyrinth is maximally of 150 microvolt that is of a lower ... with the opposite variation observed in the stimulated labyr... duration of the phenomenon is generally lower in the contra...
The results are summed up in *fig 6*

2) *Modifications induced on vestibular DC resting pot... stimulation of the efferent vestibular system*

The electric stimulation of the e v s (contralaterally ... level of the raphe) constantly caused an increase (hyp... vest DC r p

The calculation of the latency between the beginning of the stimulation of the efferent system and the beginning of the increase of the vest DC r p is not easy because of the slow beginning of the increase In our cats the estimated latencies have ranged between 9 and 12 msec

The maximal effect was reached generally within 50 100 msec, and oscillated between 100 and 200 microvolt The width of this modification usually depended on the intensity of the electric stimulation employed, though variations were to be seen in the different experimental preparations

The duration of the stimulation of the e v s was made to vary from time to time even in the same animal, although the frequency, the duration of the impulses and the intensity of the stimulus were not changed

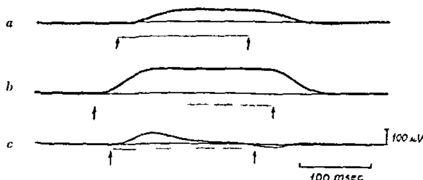


FIG 7 Three different patterns of modifications of the vestibular DC resting potentials induced by stimulation of the efferent vestibular system (area of the contralateral Deiters nucleus) Decerebrated and decerebellated cat

The arrows indicate the beginning and the end of the stimulation of the efferent vestibular system Parameters of stimulation frequency = 300 impulses/sec duration of single impulse = 0 5 msec intensity = 3 Volt

a Increase of vestibular DC resting potentials appears 9 12 msec after the beginning of the tetanic electric stimulation of the efferent vestibular system A slight decrease of the vestibular DC resting potentials may be seen during continued stimulation of the efferent vestibular system With interruption of stimulation the vestibular DC resting potentials return to their original value subsequently slightly falling under the prestimulatory level These are the most frequent experimental results

b The increase of vestibular DC resting potentials begins after a latency of 9 12 msec and reaches a plateau during continued stimulation of the efferent vestibular system without any fall with cessation of stimulation This modality is less frequent

c Slight increase of vestibular DC resting potentials during continued stimulation of the efferent vestibular system with interruption of stimulation a slight fall of resting potentials may be seen This modality was observed only in two animals

When the electric stimulus lasted for a long period (over 150-200 msec), the modifications induced in the vest DC r p behaved differently The most frequent modality of response is shown in *fig 7 a* The increase of the vest DC r p once the maximal intensity was reached would begin to decrease slowly though the stimulus lasted With interruption of stimulation the resting

potentials returned to their original values within about 75-90 msec Once they reached the basic values a slight fall of the resting potential under the prestimulatory level was observed

A modality rather often recorded is the one shown in *fig 7 b* In this case the increase of the vest DC r p remained unchanged throughout the duration of the stimulus and no fall under prestimulatory level appeared with cessation of stimulation Even in this case however, the latencies both between stimulus and the beginning of the effect and cessation of the stimulus and return of vest DC r p to their original values were very similar to those described above

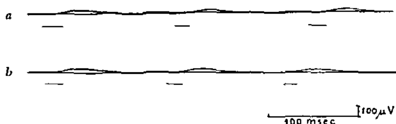


Fig 8 Effect of tetanic repetitive stimulation (Deiters nucleus region) of the efferent vestibular system on the vestibular DC resting potentials of the contralateral labyrinth
Same stimulation parameters as in previous figure
Burst of 20 msec every 150 msec continued for one minute (indicated by the short underlying lines)
a Every burst elicits an increase of vestibular DC resting potentials after a latency of 10 msec the prestimulatory level is swiftly reached every time and is followed by a slight fall
b 50 sec after continued stimulation The stimulation of the vestibular efferent system always provokes an increase of the vestibular DC resting potentials without any subsequent fall when the prestimulatory level is reached

In two animals a peculiar behaviour was observed Once the maximal effect was reached following electric stimulation of the e v s the values tended to become rapidly normal again although the stimulation continued With cessation of the stimulation an evident fall under the basic values was to be seen (*fig 7 c*)

The vest DC r p showed particular behaviour when the tetanic burst of the e v s was extremely short (20 msec) and occurred several times at regular intervals of about 150 msec, for one minute In this case every impulse was followed by a clear short hyperpolarization of the vest DC r p which disappeared quickly as the stimulus stopped and was followed by a shorter and slighter depolarization The width of the hyperpolarizing effect remained constant for every stimulus (*fig 8*)

These effects were observed especially when the contralateral region of the Deiters nucleus was stimulated The stimulation of equal intensity of the ipsi

GENERAL CONSIDERATIONS AND CONCLUSIONS

The results of these preliminary researches are still under study. Yet they seem to us to be sufficient to draw some conclusions as to the interpretation of the phenomena and their physiological meaning.

Undoubtly the activity of the e.v.s. in its peripheral part is mainly an inhibitory one on the afferent activity of the primary vestibular neurons and this action develops at the level of the neuroepithelia of the ampullary receptors. This inhibitory activity is clearly seen particularly during *tetanic stimulation* of the e.v.s.

There are however some results that lead us to conclude that the activity of the e.v.s. is actually more complex.

First of all, we have observed that the electric stimulation with *single impulses* of the e.v.s. causes the appearance of an afferent activity in the vestibular nerve, which is the expression of an excitatory phenomenon at the level of the vestibular receptors (*figs. 1* and *2*).

This effect may be explained by admitting that the activity of the e.v.s. determines first an inhibitory effect, not to be detected of course at the level of the vestibular nerve, which is followed as a rebound effect by an excitatory effect. This hypothesis may be supported by the fact that the latency between a single impulse and the appearance of the vestibular afferent spike is definitely longer (22-32 msec.) than the latency observed between the stimulation of the e.v.s. and the appearance of the hyperpolarization of the ampullary receptors (9-12 msec.) (*fig. 7*). Furthermore we must bear in mind that the tetanic burst of the e.v.s. causes the appearance of a hyperpolarization of the receptors which is followed after the cessation of the stimulus by a fall of the vest. DC r.p. *under the prestimulatory level*, which is the expression of a depolarization at the level of the receptors (TRINCKER 1959, DOHLMAN 1960, etc.).

The activity of the e.v.s. is therefore a complex one and not merely an inhibitory activity. This statement is supported by the effects that thermic stimulation of one labyrinth causes on the vest. DC r.p.

In this condition it was actually observed, as has already been said, that cold stimulation of a labyrinth hyperpolarizes the stimulated labyrinth while it contemporaneously depolarizes the contralateral labyrinth; instead warm stimulation depolarizes the stimulated labyrinth while it hyperpolarizes the contralateral labyrinth. Thus opposite phenomena occur in the two labyrinths following the stimulation of one labyrinth.

The phenomenon looks all the more peculiar when we consider that such a phenomenon occurs even under physiological conditions.

In fact an acceleration (negative or positive) determines the utriculopetal

deflection of a cupula (depolarization) and, contemporaneously, the utriculofugal deflection (hyperpolarization) of the cupula of the contralateral semicircular canal. This opposite and contemporaneous effect at the level of the vestibular receptors of the two sides seems therefore a fundamental condition in the physiology of the vestibular apparatus.

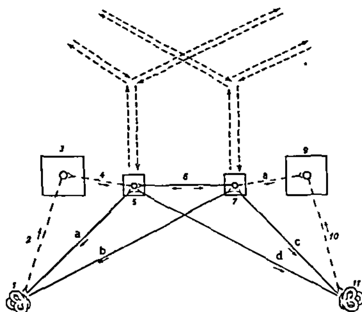


Fig. 10. Diagram of the vestibular efferent system.

Full line: efferent vestibular fibers.

Dotted and points line: afferent vestibular system.

Dotted line: polisynaptic connections of the efferent vestibular system with higher nervous centers.

1: ipsilateral labyrinthine receptors. 2: primary vestibular afferent fibers. 3: vestibular ipsilateral nuclei. 4: connections between the ipsilateral vestibular nuclei and cells of origin of the ipsilateral vestibular efferent system. 5: cells of origin of the efferent vestibular system. 6: connections between ipsilateral and contralateral vestibular efferent systems (through unknown internuncial neurons? through specific efferent fibers?). 7: cells of origin of the contralateral efferent vestibular system. 8: connections between contralateral vestibular nuclei and cells of origin of the contralateral vestibular efferent system. 9: contralateral vestibular nuclei. 10: primary vestibular afferent fibers. 11: contralateral labyrinthine receptors.

a and *c*: ipsilateral efferent fibers. *b* and *d*: contralateral efferent fibers.

Feedback systems: 1-2-3-4-5-6-7-*c*-11 (feedback loop between the two labyrinths); 1-2-3-4-5-*a*-1; 1-2-3-4-5-6-7-*b*-1; 11-10-9-8-7-*c*-11; 11-10-9-8-7-6-5-*d*-11.

On the other hand, in the case of the vestibular receptors a suitable stimulus can cause both an increase in the frequency of the spontaneous activity and a decrease and even the disappearance of this activity, which turns into excitatory and inhibitory phenomena of great functional value owing to the peculiar working mechanism of the two vestibular apparatus. Seemingly, we can infer that also *the efferent vestibular system must in its turn be capable*

SUMMARY

Experimental researches have been performed to study the modifications induced by the stimulation of the efferent vestibular system (e. v. s.) on the afferent vestibular activity recorded at the level of the vestibular nerve (v. n.) (first series of experiments) and of the vestibular receptors (second series of experiments). All experiments were carried out on cats.

In the *first series of experiments* electric stimulation of the e. v. s. was performed in the areas of the Deiters nuclei of curarized and decerebellated animals and the action potentials of the contralateral v. n. were simultaneously recorded.

The electric stimulation with single impulses caused the appearance of an afferent activity at the level of contralateral v. n. (monophasic positive and negative spikes, biphasic spikes). The latency between the stimulation of the e. v. s. and the appearance of the afferent activity was very long (22-32 msec.). The excitatory effect caused by electric stimulation with single impulses of the e. v. s. is interpreted as a rebound effect.

In other experiments the electric stimulation of the e. v. s. at tetanic frequency caused an inhibition of the spontaneous action potentials of the contralateral v. n. also when the frequency of the action potentials was increased by means of cathodic polarization of the ipsilateral labyrinth.

Some objections to this interpretation of the results obtained in this first series of experiments are discussed.

a) The action potentials recorded at the level of the vestibular nerve might be only antidromic discharges travelling along the v. n. following stimulation of the contralateral vestibular area. This possibility can be excluded by the long latency period between the stimulation of the e. v. s. and the appearance of the excitatory or inhibitory effect at the level of the contralateral nerve. This same reason can also exclude the possibility that the derivation at the level of the vestibular nerve was produced by vestibular neurons of second order. Furthermore primary vestibular fibers do not cross the midline.

b) The simple diffusion of the electric stimulation to the vestibular receptors without specific stimulation of the e. v. s. has to be rejected because of the disappearance of the above phenomena caused by midline section of the floor of the fourth ventricle and by the fact that the stimulation of only certain points is capable of producing the above mentioned modifications.

c) Electric activity of the v. n. could be derived not only from the axis

cylinders but also from cell bodies scattered throughout the nerve fibers that is the phenomena which we observed could be due to interneuronic influence among vestibular fibers of second order. This objection may be excluded because these cells belong functionally to Scarpa's ganglion, that is they are first order neurons.

The *second series of experiments* was performed on precollicolarly decerebrated and sometimes also decerebellated cats to study the modifications induced by the stimulation of the e.v.s. on the vestibular DC resting potentials (vest. DC r. p.) of the ipsilateral and contralateral labyrinth. The following procedures were employed: *a*) thermic (cold and warm water) stimulation of one labyrinth and contemporaneous recording of DC r. p. of both labyrinths; *b*) electric tetanic stimulation of the e.v.s. and simultaneous recording of DC r. p. of the ipsilateral and contralateral labyrinth; *c*) electric stimulation of the e.v.s. performed as soon as the thermic stimulation of the recorded labyrinth had caused the maximal modifications of the vest. DC r. p.; *d*) strychnine intravenously administration in order to study its effect during stimulation of the e.v.s.

The following results have been observed:

a) Thermic stimulation with warm water of one labyrinth causes depolarization of this same labyrinth and simultaneously hyperpolarization of the contralateral labyrinth; cold water stimulation causes a reverse effect. This demonstrates that there is a closed feedback loop between the two labyrinths.

b) Electric stimulation of the e.v.s. always causes hyperpolarization of the DC r. p. both of the ipsilateral and contralateral labyrinth.

c) Electric stimulation of the e.v.s. performed as soon as the thermic stimulation had caused the maximal modifications of the vest. DC r. p. increases the hyperpolarization generated by the cold water stimulation and reduces the depolarization generated by the warm water stimulation.

d) Strychnine intravenously administration reduces or abolishes the above effects caused by stimulation of the e.v.s.

These results lead to the conclusion that the e.v.s. is capable of performing a modulating activity on the vestibular impulses with an excitatory and inhibitory effect according to the functional state of the receptors.

Likewise the A. suggests that efferent vestibular centers of the brain stem and efferent fibers reaching labyrinthine receptors are to be considered the terminal part, more peripheral and anatomically more easily demonstrable, of a specific polisynaptic system as it was demonstrated for the olfactory and auditory efferent systems.

These preliminary results allow us to consider under a new light some common observations in human pathology and constitute the physiological basis for the psychosomatic interpretation of some troubles of the labyrinthine function.

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S U P P L E M E N T U M 196

NOISE INDUCED HEARING LOSS AMONGST ENGINEROOM PERSONNEL ON BOARD NORWEGIAN MERCHANT SHIPS

BY

SVERRE QUIST-HANSSEN

ACTA OTO-LARYNGOLOGICA · KARLAVÄGEN 41, STOCKHOLM Ö

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SUPPLEMENTUM 196

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A W BRØGGERS BOKTRYKKERI A/S - OSLO

NOISE INDUCED HEARING LOSS AMONGST ENGINEROOM PERSONNEL ON BOARD NORWEGIAN MERCHANT SHIPS [1]

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Abstract

The aim of the investigation was to elucidate to what extent noise induced hearing loss in Norwegian merchant ship's engine personnel is caused by exposure to noise from diesel engines. The majority of 65 men examined had been exposed to workshop noise and diesel engine noise, some also to other kinds of noise harmful to hearing. Ten ears in seven men had to be discarded. Three had conductive hearing loss, seven sensori neural hearing loss of non-occupational causes.

Hearing loss in the remaining 120 ears distributed in 62 men must have been caused by workshop noise, diesel engineroom noise, or both.

Hearing loss induced by workshop noise could be shown to increase with increasing intensity of the noise and duration of employment, as is generally known.

By calculation of the hearing loss risk incurred during workshop employment by the group exposed to both kinds of noise it could be shown that the hearing loss induced by diesel engine room noise must be faint. Examination of a small group exposed to diesel engineroom noise only supports this assumption.

The main cause of hearing loss from diesel engineroom noise seems to have been impact noise from safety valves or produced when indicating diagrams are made.

Technical noise abatement procedures may presumably eliminate hearing loss risk produced by the steady state noise in merchant ships' diesel engineroom. Engineroom crews must, however, protect their ears against impact noise from safety valves or produced when indicating diagrams are made.

During the last decade the diesel engine and the steam turbine engine have displaced the steam piston engine as the main propelling force in the Norwegian mercantile marine. The diesel engine, which makes a considerable noise, is the source of energy both for propulsion and for auxiliary machines in most Norwegian merchant ships today.

In the Navy it was early realised that the loud noise made by the diesel engine represented a danger to the hearing of engine room crews. As early as 1942 Schilling and Everley [3] and de Witt [47] reported that they had found noise induced hearing loss in engine room crews serving in submarines. In 1955 Lund-Iversen [24] reported on the noise on board Norwegian submarines and motor torpedoboats and its effect on the hearing of engineroom crews. His findings

[1] Det norske maskinistforbund (Norwegian engineer officers' organization) has given financial support to the investigation and O. W. Tenfjord M.D., the Medical Office for Seamen, Oslo has assisted in providing the material.

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agreed with those of Schilling and Everley, and de Witt, and were confirmed by Webster and Solomon[45] the same year

Schilling and Everley found serious induced hearing loss in personal having more than 16—20 years service with diesel engines at a noise of 112—126 dB Lund Iversen demonstrated noise induced hearing loss in $^1/_5$ of crews who had been exposed to noise of 100—112 dB in the enginerooms of submarines and to 102—124 dB in the enginerooms of motor torpedoboats In $^2/_3$ of the cases however, the hearing loss was slight, and the crews had been exposed to acoustic traumas previous to their engineroom service

In 1959 Ahlborg[3] reported that an investigation he had made of 120 engineer officers in the mercantile marine revealed noise induced hearing loss in $12^1/_2$ per cent He stated, however, that the investigation "should in no way be taken as answering the question of where the engineroom crews acquire their noise induced hearing loss" The hearing loss could have arisen 'e g during military service, private shooting practice or during work as a controller or apprentice at a shipyard etc"

Schilling and Everley found noise induced hearing loss where the noise from the diesel engine in the engineroom of a submarine was the only auditory trauma the crews had been exposed to, and Coles and Knight[7] found a similar hearing loss amongst workers in testrooms for diesel engines Webster and Solomon's results pointed to greater noise induced hearing loss amongst submarine engine room crews than other submarine crews with the same length of service on sub marines To what extent crews working year after year in the enginerooms of diesel driven merchant ships incur the risk of impaired hearing is, however, an open question

In order to throw light on this question a group of men who have served in enginerooms on board ships of the Norwegian mercantile marine have been examined

From investigations of the hearing of industrial workers it is well known that their loss of hearing may have other causes than the noise arising from their occupation[14, 29] In the present material therefore an attempt has been made by means of detailed anamnesis and the collection of other information to bring to light all factors which might have contributed to a loss of hearing

1 *Congenital hearing loss* which occasionally occurs in the frequency range above 1000 cps does not seem to be present in any of the persons examined Nor do their anamneses or pure tone audiograms point to *familial hearing loss*

2 *Head injuries* may give rise to hearing loss of noise induced pattern[31] Eleven of the 65 men examined had suffered head injury, leading to un consciousness in nine cases, one of which had incurred a skull fracture In only one case and one ear is there reason to believe that the head injury has resulted in hearing loss This one ear has therefore been rejected from the material

3 *Diseases of the ear* Eleven of the men examined had previously suffered from acute otitis Nine had incurred no permanent injury Two had scars on one eardrum Of these one had normal hearing, the other a slight conductive

hearing loss. One man had otosclerosis in both ears with considerable hearing loss of a purely conductive nature.

There has not been complete agreement as to the significance conductive hearing loss has for the reaction of the ear to auditory traumas. There seems, however, to be grounds for believing that it affords some protection against noise induced hearing loss as Theilgaard[41] has shown. The three ears with conductive hearing loss have therefore been rejected from the material.

4. *Non occupational auditory traumas.* Hearing loss caused by impact noise occurs even in childhood[4] but arises more frequently in maturity, particularly during military service[1, 28, 31, 36]. Considering the slight hearing loss found after a comparatively large amount of shooting[6, 11, 18, 39], it is improbable that the extremely modest amount of shooting the engineroom crews in the majority of cases have done could have caused hearing loss of any importance. Loss of hearing induced by impact noise has been shown to correspond well with the anamnestic information about subjective hearing loss and tinnitus in connection with shooting[34, 42]. In contrast to hearing loss from exposure to occupational steady state noise, impact noise injures often only one ear and occurs particularly at the frequencies above 4000 cps[34]. Building on these findings, an attempt has been made to identify and exclude in the material examined the hearing loss induced by impact noise and explosions.

Private shooting. Four men have done a little game and range shooting. One has impact noise induced hearing loss in one ear which has therefore been discarded.

Military shooting. 23 men have taken part in light arms firing practice, the majority only to a very modest extent. One has done considerably more shooting than the others but has not noticed any particular hearing loss or tinnitus after the shooting. Since he has been exposed to both workshop noise and several years noise in diesel enginerooms he has not been excluded from the material. (See later.)

Explosions. Seven men have been exposed to gunfire or explosions on board. During gunfire all had put their fingers in their ears as a protection. One man only stated that he could not hear for several minutes after gunfire. He has been neither in a diesel engineroom nor in a workshop, has normal hearing in one ear and incipient hearing loss of noise induced pattern in the other ear. Five men have been exposed to explosions in the engineroom or in the hold. In one case there is reason to assume that a violent explosion has been the main cause of hearing loss and this case has therefore been removed from the material.

Other non occupational auditory traumas. Twelve men have been exposed during military service to noise from jet planes or diesel engines. The exposures have lasted a short time, there have been long intervals between them and all the men have used ear protectors permanently. As six have normal hearing in both ears and three have an incipient noise induced hearing loss there is no reason to assume that these auditory traumas have been of significance in the three remaining cases where there is a greater degree of hearing loss. No allowance has therefore been made for this special military service.

Of the 130 ears of the 65 men examined the following are therefore rejected
3 ears with conductive hearing loss
1 with hearing loss after a head injury
1 with impact noise induced hearing loss after rifle shooting
2 with hearing loss after explosion

A further 3 ears with sensori-neural hearing loss but not of noise induced pattern must also be discarded, 2 ears belonging to one man, one to another

Thus a total of 10 ears belonging to 7 men have been rejected There remain 120 ears, distributed over 62 men, where it must be assumed that hearing loss will have been caused by exposure to occupational noise either in a workshop during training or during supervision of newbuilds and repair and during service in enginerooms on board ships in the mercantile marine

It is the chief engineers with many years service in enginerooms and workshops who supervise newbuilds and repairs Only one of these men has been so much exposed to loud noise during such supervision that there are grounds for adding this noise exposure to the exposure he has undergone in workshops

At sea chief engineers are only for short periods at long intervals in the engineroom, service which must be regarded as of minor importance to the hearing compared with the ordinary watches of 4 + 4 hours noise exposure per day with noise free intervals of 8 hours Regular overtime in enginerooms has not occurred to an extent of any importance for the hearing

It must therefore be assumed that hearing loss amongst the engineroom personnel examined is due to workshop noise, noise in diesel enginerooms or both

The majority of the men examined have themselves while in workshops used pneumatic tools or have been exposed to riveting noise during the installation of machinery in newbuilds Some have been in a smithy Only a few have not been exposed to noise in a workshop at all Some have been exposed to noise of moderate intensity, others at times to noise of high intensity, many only to noise of high intensity the whole of the period they have been in workshops

The material has been divided into three groups based on detailed information about working conditions during their period of employment in workshops Those who during the whole of their workshop period have been exposed either to "noise of high intensity" only, or to "noise of moderate intensity" only make up the two extremes and those who have been exposed to "noise of medium intensity" form a less homogeneous middle group

25 men have been exposed to noise of high intensity during the whole of their workshop period Four, however, had used ear protectors permanently These four are therefore placed in the group "noise of moderate intensity" together with 14 men who had not been exposed to noise of high intensity at all while in workshop 19 men, during the whole of their workshop period have been exposed to noise the intensity of which has been between the two extremes These 19 men are placed in the group "noise of medium intensity" The "high intensity noise" group thus consists of 21 men, the "moderate intensity noise" group of 18 men and the "medium intensity noise" group of 19 men, a total of 58 Four men had not been in a workshop

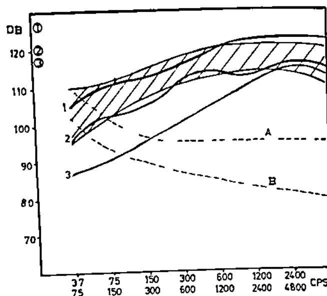


Fig 1 Noise in boiler shops and shipyards

1 Staybolt riveting (Vikdal)
2 Hammering out nails (Vikdal)
3 Riveting of nails (Vikdal)

Noise in workshops Riveting caulking and chiselling w constitute the dominating noise The sound pressure of thi between 110 and 128 dB [43], the major part being in the fre 600 cps [19, 43] as shown in Fig 1

Noise in ships' enginerooms The engineroom personnel ex on board merchant ships propelled by steam piston engines s or diesel engines

Steam piston engines Information about the noise fro scanty Slawin [35] records 77—88 phon for three ships, Vatz 85 dB Since the sound pressure is low and the greather p the low frequency range, noise in a steam piston engineroo as harmless to the hearing But where ships with steam pist diesel auxiliary engines service on board has been counted engined ships since auxiliary diesel engines make just as mu engines [40 b]

Steam turbine engines The greatest sound pressure from throughout between 500—1000 cps (* ² ³⁹, ⁴⁰ ᵃ, ᶜ) Storm fo of 100 dB(C) in one ship Van Os found the sound pressure reduction gears to be considerably higher (see Fig 2) In pattern and the total sound pressure noise from steam considered harmful to the hearing though to a far le

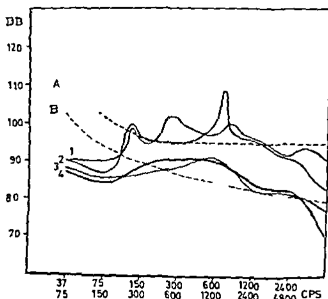


Fig 2 Noise in steam turbine enginerooms
1, 2, 3, three ships (1/3 octave band analysis, van Os)
4 one ship (octave band analysis, Storm)
A Boundary for risk of hearing loss (Rosenblith and Stevens)
B Boundary for risk of hearing loss (Noise Rating Curve 85)

workshops and from diesel engines Eight men have served in steam turbine ships but only six with full watches in the enginerooms Five of these have served for periods up to 6 years but have been exposed to noise of high intensity in workshops and diesel enginerooms as well to a degree that makes this latter exposure the more important In only one case is it possible that the hearing has been affected by noise from steam turbine engines — a case with 15 years service in steam turbine ships, less than a year in diesel engine ships and 3 years in a workshop with high intensity noise Noise from steam turbine engines has not therefore been taken into consideration as causing hearing loss in engineroom personnel who have been in workshops or in ships with diesel engines

Noise from diesel engines Noise in a diesel engineroom is due just as much to the auxiliary engines as to the main engines [40 b] The size of the main engine does not seem to effect the sound pressure of the noise [40 c] High speed engines usually make more noise than low speed engines but there is considerable variation [35, 40 l] Noise in diesel enginerooms usually has much higher sound pressure than noise from steam turbine engines and greater energy in both low and high frequencies but more especially in the low frequency range The data for Norwegian diesel ships given by Storm talley well with those given by Cook and Fleming for diesel engines with superchargers and with the author's finds in cooperation with G Flottorp for two diesel ferries One must reckon with a sound pressure of 104—115 dB C, 100—108 dB B and 98—106 dB A with a considerable part of the energy in the frequencies above 1000 cps (Fig 3)

Damage to hearing from occupational noise How harmful a steady state noise

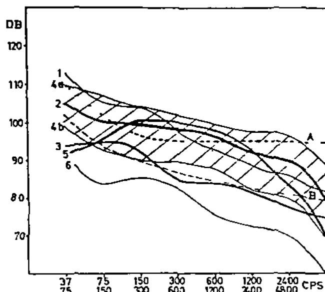


Fig 3 Noise in diesel ships enginerooms at manoevring stand
1 and 3 for two ships (van Os)
2 mean for 15 ships (Storm)
4a—b in 24 ships (Storm)
5 Diesel ferry (author)
6 same ferry, enclosed manoevring stand
A Boundary for risk of hearing loss (Rosenblith and Stevens)
B Boundary for risk of hearing loss (Noise Rating Curve 85)

is depends on its sound pressure, frequency spectrum and the duration of exposure to it Experimental data and the results of investigations of workers in noisy surroundings mostly agree as to the boundary between noise injurious and not injurious to hearing ([19], [20], [22], [23], [44]) Fig 4 gives a comparison of various "Damage Risk Criteria" The frequency pattern of the individual curves are basically alike and indicate that at the same total sound pressure low frequency noise is less harmful to the hearing than high frequency noise There is, however, a difference in sound pressure level between the Slawin criterion and the criterion proposed by Eldrid et al [10], Kryter [23], and Rosenblith and Stevens [32] Between these two lies Hardy's "50 sones per octave" criterion [19] and the closely related Hinchliffe's criterion [20], the Noise Rating Curve 85 proposed by Glorig et al [16], and Kylin s criterion zone [2?], the lower level of which conforms with Slawin's criterion [38]

Rosenblith and Stevens state that an adequate specification of a Damage Risk Criterion is a complicated matter involving many variables They are of the opinion that a level 10 dB below their criterion "would involve negligible risks indeed' whereas 10 dB above 'would result in significant increases in hearing loss' Eldrid et al consider that sound pressure up to the criterion they have proposed «may result in hearing loss only in the most sensitive individuals" About his criterion zone Kylin states that it is a zone 'below which no or insignificant hearing loss occurs" after prolonged exposure to steady state noise

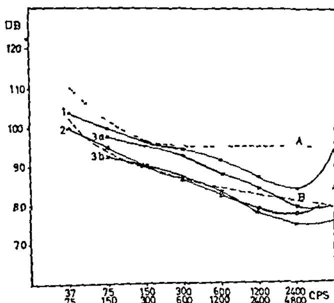


Fig 4 Boundaries for sound pressure of steady state noise not harmfull to hearing full working day, year long exposure Damage Risk Criteria

A Kryter, Rosenblith and Stevens
B Noise Rating Curve 85 (Glorig et al)
1 50 sones per octave (Hardy)
2 Slawin
3a—b Kylin

Exposure time The Damage Risk Criteria shown in Fig 4 are all made on the assumption of noise exposure for a full 8 hours day, 5—6 day week, year in year out, "a lifetime exposure" At sea engineroom crews' watches are 4 hours followed by 8 hours off duty without noise This division of working hours reduces the harmful effects of the noise [16, 37], likewise reduced noise intensity and more frequent noise free intervals when in port, and the longer noise free periods during holidays, courses etc [40], which have been common in the material examined With this in mind Rosenblith and Stevens' Damage Risk Criterion can be accepted with greater certainty as a basis when estimating the harmful effect on hearing of engineroom noise than when estimating the effects of workshop noise

As shown in Fig 2 the noise from steam turbine engines lies, though in places a little above, mostly below Rosenblith and Stevens' Damage Risk Criterion In diesel ships, however (Fig 3), it lies at an average 10 dB above, with relatively greater energy in both base and treble The sound pressure of noise from riveting and similar operations with pneumatic tools (Fig 1) which constitutes the predominant part of high intensity workshop noise is approximately 10 dB greater than the sound pressure of diesel engine noise and has furthermore the greater part of its energy in the frequencies above 600 cps The damage a noise does to hearing increases in proportion to the number of dB the noise, in any octave-band rises over 85 dB [44] On the basis of Rosenblith and Stevens' Damage Risk

Criterion one must assume that noise from steam turbine engines represents little danger, diesel engine noise greater danger and the high intensity workshop noise decidedly the greatest danger to hearing

Noise induced *hearing loss occurs mostly during the first years of exposure* to injurious noise, especially for the age groups over 26 years[11, 16] In view of the sound pressure and frequency spectrum of the noise, one is therefore justified in placing together in one group those who have served 15 years or more on board diesel ships and those who have been 5 years or more in workshops

The material consists of 62 men who have served in enginerooms in ships of the Norwegian mercantile marine Seven have not been in diesel ships Five of the 55 who have been in enginerooms in diesel ships have only had from 4 to 10 months service there These five have been in workshops, one for 4 years in noise of moderate intensity and the remaining four from 2 to 14 years in noise of high intensity It must be assumed that the noise exposure in diesel ships for less than a year has been without importance for these five men compared with the noise exposure in workshops They are therefore grouped with the seven men who have not been in diesel ships Thus 12 men have either been less than one year in diesel ships or not at all 50 men have been in diesel ships for a year or more Three of these have not been in workshops at all while the remaining 47 have been in workshops for one year or more

Fig 5 shows the distribution of the material according to the number of years service in diesel ships in relation to the number of years spent in workshops exposed to noise of high, medium and moderate intensity Over half of those who have been 4 years or more in workshops have been exposed to noise of

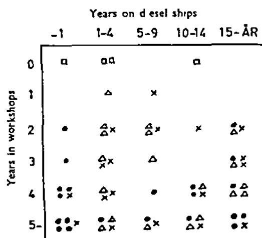


Fig 5 Distribution of 62 engineroom personnel according to *no of years service on diesel ships* in relating to *no of years in workshops* exposed to noise of

● high
△ medium
× moderate
} intensity

□ indicates no workshop period

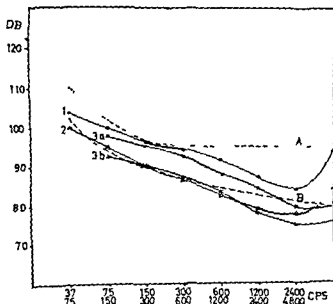


Fig 4 Boundaries for sound pressure of steady state noise not harmfull to hearing full working day, year long exposure Damage Risk Criteria

A Kryter, Rosenblith and Stevens
B Noise Rating Curve 85 (Glorig et al)
1 50 sones per octave (Hardy)
2 Slawin
3a—b Kylin

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One man was examined 3 hours after he had left the diesel engineroom with only a small part of the machinery running. The others were examined 12 hours or more after their last exposure to noise. The hearing loss must therefore be assumed to be permanent.

Table III shows the age distribution of the material.

Table III *Age distribution (62 men)*

Age in years	—20	21—30	31—40	41—50	51—60	61—	Total
Number	1	13	15	12	14	7	62

Seven eighths of the material are between 21 and 60 years old evenly distributed throughout the decades.

In order to be able to compare the hearing of individuals of different age groups a corrective must be introduced for the physiological reduction in hearing which accompanies age[13]. The results from various investigations of this subject agree closely[9, 13, 14, 15, 21, 30]. Divergences may be due to variations in the composition of the material, differences in the normal hearing threshold taken as starting point, the audiometry technique and the circumstances of the examination[9]. The correction data selected for the engineroom crews under consideration are based on the investigations of Hinchcliffe with the dB figures for the various frequencies and decades as given in table IV.

Table IV *Presbyacusis corrections*

Age in years	Hearing loss in dB at the frequencies 1	2	3	4	6 kc
40—49	3	3	8	9	8 dB
50—59	5	7	12	15	15 »
60—69	10	12	17	21	27 »

These data evaluate conservatively the part played by presbyacusis in hearing loss and ensure that the significance of the occupational noise is given its full weight. The presbyacusis corrected audiograms are graded for degree of hearing loss as follows:

Noise induced hearing loss

degree 0 — hearing loss under 20 dB at 2—6 kc
I — » » of 25—40 dB at 3 4 or 6 kc
II — » » over 40 dB at 3 4 or 6 kc
III — » » over 40 dB at 3 4 or 6 kc and over 20 dB at 2 kc

Exposed to workshop noise but not to diesel engine noise

As stated previously 12 men have either not served in diesel ships or have served less than a year 11 of these men have been in workshops 10 have worked in high intensity noise One of these has used ear protectors permanently and is therefore placed, together with one other man who has been exposed, without ear protection, to noise of moderate intensity only, in the "noise of moderate intensity" group The relation between number of years in workshops and degree of hearing loss in 21 ears in 11 men is shown in Table V

Table V *Relation between no of years in workshops and degree of hearing loss in 21 ears (11 men)*

Degree of hearing loss	Years in workshops 1	2	3	4	5—	Total
0				2x		2
I		2		3	2y	7
II			1z	1	4	6
III			1z	2	3	6
						21 ears

Of the 22 ears in the 11 men one ear, where the hearing loss can not be classified as noise induced, has been rejected Allowing for the small numbers, the degree of hearing loss rises steadily with increasing number of years in workshops As mentioned earlier it is possible that 15 years service in steam turbine ships may have been a contributory cause to hearing loss in 2 ears (marked z) which after 3 years of workshop noise of high intensity have a hearing loss of IInd and IIIrd degree One man with normal hearing after 4 years of workshop noise of high intensity (marked x) has constantly used ear-protectors and one man (marked y) with a hearing loss of Ist degree after 5 years in workshops has been exposed to noise of moderate intensity only

Exposed to noise in dieselships but not in workshops

Only 3 men come in this group One has normal hearing in both ears after 2 years service, one has a hearing loss of 25 dB at 4000 cps in both ears after 10 years service The third has a hearing loss of impact noise induced pattern after 3 years service None of the three had used earprotectors

Exposed to noise both in workshops and in diesel ships

47 men have been one year or more both in workshops and in diesel ships The intensity of their exposure to workshop noise, their number of years service in diesel ships and in workshops appear from Fig 6 The relation between the latter ignoring the intensity of the workshop noise, is shown in Table VI

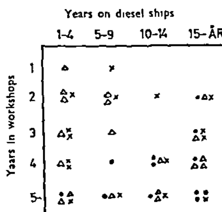


Fig 6 Distribution of 47 men engineroom personnel according to *no of years service on diesel ships* in relation to *no of years in workshops* exposed to noise of

● high
△ medium
× moderate
} intensity

Table VI *Relation between no of years on diesel ships and in workshops (47 men)*

Years in workshops	Years of service on diesel ships 1—4	5—9	10—14	15—	Total
1	1	1			2
2	3	3	1	3	10
3	3	1		4	8
4	3	1	4	4	12
5—	4	3	4	4	15
	14	9	9	15	47 men

It appears from Fig 6 that an undue proportion of those with the longest service in diesel ships have been exposed to noise of high intensity, 3 out of 9 in the group 10—14 years, 6 out of 15 in the group 15 years or more The average time in workshops spent by each diesel ship group appears from Table VII

Table VII *Average time in workshops for each diesel ship group (47 men)*

Years in workshops	Years of service on diesel ships 1—4	5—9	10—14	15
mean	3 4	3 2	4 2	3 6
median	3 5	3	4	4

The average time spent in workshops by all diesel ship groups taken together is 3 6 years with extremes 3 2 and 4 2 years Excluding two men who have been only one year in workshops, the average number of years service in diesel ships of each period of employment in workshops is shown in Table VIII

Table VIII *Average time in diesel ships for each workshop group (45 men)*

Years in diesel ships	Years in workshops 1	2	3	4	5—
mean		8 8	9 5	10 7	9 0

The average number of years service in diesel ships for each group with a period of employment in workshops over a year is approximately 9 5 with extremes of 8 8 and 10 7 With due allowance for the small numbers involved, no correlation between number of years in workshops and number of years service in diesel ships appears

As stated previously, under otherwise equal conditions, the injurious effect of noise on hearing increases with the sound pressure of the noise When assessing for each diesel ship group the effect of workshop noise on the hearing, in addition to the duration of the exposure, the mean intensity of the noise must be taken into consideration

It must be assumed that the noise of high intensity has been considerably more harmfull to hearing than the noise of medium and moderate intensity In can therefore be weighted with the compensating factor 4 as against 2 for noise of medium intensity and 1 for noise of moderate intensity Table IX shows the calculated mean intensity of the workshop noise for each workshop group

Table IX *Calculated mean intensity of workshop noise for each workshop group (58 men)*

Workshop noise intensity	Years in workshops 1	2	3	4	5—
mean	1 5	1 8	1 8	2 4	2 5

It appears from Table IX that those who have been the longest time in workshops have also been exposed to noise of a higher intensity than those with a shorter time in workshops The degree of hearing loss disclosed for each workshop group appears from Table X

Table X *Degree of hearing loss for each workshop group (112 ears in 58 men)*

Degree of hearing loss	Years in workshops 1	2	3	4	5—
0	3	11	4	5	4
I	1	9	11	8	7
II			2	10	16
III		2x	1	9	9

Excluding the two ears marked x where other auditory traumas (rifle shooting) may have contributed considerably to the hearing loss the average hearing loss for each workshop group is found to be as shown in Table XI

Table XI *Average hearing loss for each workshop group (100 ears in 57 men)*

Degree of hearing loss	Years in workshops 1	2	3	4	5—
mean	0 25	0 3	0 8	1 8	1 7

With due reservation for the small numbers the table shows a steady rise in degree of hearing loss corresponding to the rise in number of years in workshops In Table XII the relative mean degree of hearing loss for each workshop group is seen in relation to the relative mean intensity of noise exposure

Table XII *Relative mean degree of hearing loss in relation to relative mean intensity of workshop noise exposure (57 men)*

	Years in workshops 1	2	3	4	5—
(A) Relative mean hearing loss	1	1 2	3 2	7 2	6 8
(B) Relative mean intensity of noise exposure	1	1 2	1 2	1 6	1 7
(A) (B)	1	1	2 7	4 5	4 0

Taking into account the limited extent of the material the age distribution and the weighting for the intensity of the noise exposure the increase in hearing loss with increasing exposure revealed in Table XII accords well with the results of Glorig Grings and Summerfield

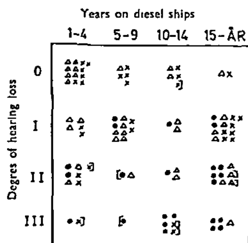


Fig 7 Distribution of 91 ears according to degree of hearing loss, no of years service on diesel ships and exposure to workshop noise of

- ● high
- △ medium } intensity
- × moderate
- ⊐ exposed to impact noise from safety valves and indicating"
- ⊏ examined 3 hrs after cessation of noise

50 men (97 ears) have served one year or more in diesel ships but only 47 of them have also been one year or more in workshops Fig 7 shows for the 91 ears in the 47 men, the intensity of the noise exposure during their time in workshop and the degree of hearing loss for each diesel ship group

Table XIII gives the degree of hearing loss for each group of service on diesel ships, ignoring the degree of noise intensity experienced in the workshop

Table XIII *Degree of hearing loss for each diesel ship group (91 ears)*

Degree of hearing loss	Years on diesel ships 1—4	5—9	10—14	15—	Total
0	13	5	5	2	25
I	5	10	3	13	31
II	7	2	3	9	21
III	2	1	6	5	14
Mean	0 9	0 9	1 6	1 6	

For it to be possible to assess the effect on hearing of the noise in diesel enginerooms the average hearing loss shown for each diesel ship group must be corrected for the influence of workshop noise The mean intensity of workshop noise for each diesel ship group is shown in Table XV

Table XIV *Mean intensity of workshop noise for each diesel ship group*

	Years on diesel ships			
	1—4	5—9	10—14	15—
Workshop noise intensity, mean	1 7	2 1	2 3	2 6
Years in workshops, mean	3 4	3 2	4 2	3 6

The product of the mean intensity and duration of the noise exposure may express the workshop conditioned risk of hearing loss for each diesel ship group. The product of the relative mean noise intensity and the relative mean exposure time together with the relative mean degree of hearing loss appears from Table XVI.

Table XV *Workshop conditioned risk of hearing loss and relative diesel engine conditioned hearing loss for each diesel ship group*

	Years on diesel ships			
	1—4	5—9	10—14	15—
(A) Relative intensity of workshop noise	1	1 2	1 4	1 5
(B) Relative duration of workshop employment	1 1	1 0	1 3	1 1
(A B) Relative workshop conditioned hearing loss risk	1 1	1 2	1 8	1 7
(C) Relative mean hearing loss	1	1	1 8	1 8
(C/A B) Relative diesel engine conditioned hearing loss	0 9	0 8	1 0	1 1

It is evident from Table XVI that in the material examined there is little or no increase in hearing loss with increasing number of years service on dieselships when the workshop conditioned risk of hearing loss of each group is taken into account.

As previously stated 58 men (112 ears in the material) have been one year or more in workshops. Fig. 8 shows for the 112 ears the intensity of noise during their workshop period, number of years in workshops and degree of hearing loss. The calculated intensity of the workshop noise for those exposed to noise of either medium or moderate intensity is on an average the same. The mean hearing loss for the workshop groups exposed to moderate or medium workshop noise is then as in Table XVII.

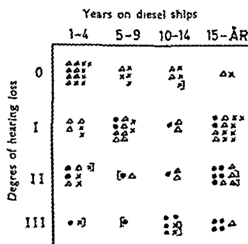


Fig 7 Distribution of 91 ears according to *degree of hearing loss no of years service on diesel ships* and exposure to workshop noise of

● high } intensity
Δ medium
× moderate
] exposed to impact noise from safety valves and indicating
[examined 3 hrs after cessation of noise

50 men (97 ears) have served one year or more in diesel ships but only 47 of them have also been one year or more in workshops Fig 7 shows for the 91 ears in the 47 men, the intensity of the noise exposure during their time in workshop and the degree of hearing loss for each diesel ship group

Table XIII gives the degree of hearing loss for each group of service on diesel ships, ignoring the degree of noise intensity experienced in the workshop

Table XIII *Degree of hearing loss for each diesel ship group (91 ears)*

Degree of hearing loss	Years on diesel ships 1—4	5—9	10—14	15—	Total
0	13	5	5	2	25
I	5	10	3	13	31
II	7	2	3	9	21
III	2	1	6	5	14
Mean	0 9	0 9	1 6	1 6	

For it to be possible to assess the effect on hearing of the noise in diesel enginerooms the average hearing loss shown for each diesel ship group must be corrected for the influence of workshop noise The mean intensity of workshop noise for each diesel ship group is shown in Table XV

of medium intensity, the relation between mean hearing loss and the number of years in workshops is found to be as shown in Table XVIII

The workshop noise of medium and moderate intensity has thus given rise to a small but steady *increase of hearing loss during the first four years in work*shops and a slightly larger increase later By comparison, for those who have been exposed to workshop noise of high intensity the mean hearing loss is as shown in Table XIX

Table XVIII *Mean hearing loss for workshop group exposed to high intensity noise*

High intensity workshop noise group

	Years in workshops				
	1	2	3	4	5—
Mean hearing loss		2	2	2 4	2 5

The hearing loss occurs mostly during the first years of exposure to the work shop noise of high intensity and is considerably greater than among those ex posed to noise of medium and moderate intensity Tables XVII and XVIII give grounds for assuming that impact noise from safety valves and "indicating" in diesel enginerooms has constituted a certain danger to the hearing

Given the small numbers, the material seems to show, as generally known that the hearing loss increases with increasing intensity of noise and increasing number of years in workshops The steady noise in diesel enginerooms on ships of the merchant navy seems to have constituted little or no danger to the hear ing There is, however, reason to assume that impact noise from safety valves and '*indicating*" *has caused hearing loss*

Auditory impairment in connection with noise induced hearing loss

The goal of the prevention of hearing loss from noise exposure must, as previously stated be to hinder the occurence of damage which impairs the ability to understand everyday speech [16] Noise induced hearing loss occurs primarily in the frequencies above 2000 cps where even considerable hearing loss does not impair the ability to understand everyday speech [16, 30] Hearing loss at 2000 cps may also exist without impairing this ability [29, 31] It is only when a third degree hearing loss arises that one can expect to find the understanding of speech im paired 21 of the 62 men comprising the material complained of difficulties in understanding everyday speech more especially in the presence of noise or when several people were speaking at once Table XX shows how both complainants and non complainants were distributed with regard to age and degree of hear ing loss

Table XIX *Subjective degree of hearing loss in relation to age (62 men)*

left of dash — complainants
right of dash — non-complainants

Hearing loss	Age —20	21—30	31—40	41—50	51—60	61—	Total
0	0/1	1/14	1/0	1/0	1/0		4/15
I		0/18	1/0		1/0		2/18
II		0/8	1/0	1/0	5/0	2/0	9/8
III			1/0		3/0	2/0	6/0
	0/1	1/40	4/0	2/0	10/0	4/0	21/41

The table shows that difficulty in understanding everyday speech increases with the degree of hearing loss and with increasing age Those who with normal hearing or with hearing loss of first degree in one ear have complained of difficulty in understanding speech have regularly had a greater hearing loss in the other ear It must be assumed that centrally conditioned hearing difficulties begin to make themselves felt among those with a hearing loss of second degree since it is mostly the older ones who complain In eight men with a hearing loss of second or third degree, speech audiometry with a three digit test and mono syllabic PB word lists has been carried out (Quist Hanssen's word lists) The eight best ears showed a threshold shift of 50—55 dB for monosyllabic PB word lists, and full discrimination but a somewhat protracted discrimination curve Four of the eight men complained of impaired understanding of speech, four did not Those who complained were between 52 and 60 years old, those who did not were 27, 37, 40 and 66 years old

Prevention of hearing loss amongst engineroom personnel in the merchant navy

In order to have prevented hearing loss in the engineroom personnel examined, it would have been necessary, first and foremost, to have protected their hearing from the loud noise in workshops, particularly in shipyards The steady state noise in the enginerooms of diesel ships seems to have had but little injurious effect on the hearing of the crews (In the majority of engineers workshop noise exposure has preceded the exposure to diesel engineroom noise The effect of the latter has therefore predominantly been restricted to the induction of additional hearing loss) There is, however, reason to assume that impact noise from the safety valves of the diesel engines and the "indicating" are exposures against which the ears must be protected There are therefore good grounds for using ear protectors during service in diesel enginerooms Since damage from the steady state noise, however, seems to be of modest dimensions any reduction of the noise will contribute considerably to lessen its harmful effect It can therefore be assumed that technical steps aimed at preventing

damage from noise generally ([1], [8], [25], [40b], [46], [48]) would make a useful contribution to reducing the risks of hearing loss in diesel enginerooms, and possibly eliminate them

Conclusions

1 The hearing loss of the engineroom personnel examined is primarily due to the loud noise they have been exposed to during their period of employment in workshops, particularly in shipyards
2 The harmful effect on the hearing of steady state noise in the diesel engine rooms seems to have been small
3 Impact noise from safety valves of diesel engines and the "indicating" has increased the danger of hearing loss
4 Hearing loss due to noise from diesel engines has been limited and of no importance for the understanding of everyday speech
5 During service in diesel enginerooms ear protectors should be used
6 Since impact noise must be assumed to constitute a main cause of hearing loss in *diesel enginerooms glassdown ear protectors* are to be recommended [12]
7 Whether ear protectors are used or not the personnel of enginerooms in diesel ships should have their ears examined audiometrically before commencing service and checked at intervals afterwards
8 Since the steady state noise in diesel enginerooms has entailed little danger of hearing loss, the general preventive action of technical noise abatement should render individual ear protection superfluous, except when indicating diagrams are made

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MITTEL- UND INNENOHRVERÄNDERUNGEN NACH OPERATIVEN MANIPULATIONEN AM STAPES; EINE TIEREXPERIMENTELLE STUDIE

VON

F. SCHWETZ

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So kurz die Ära der Steigbügeloperationen auch ist, reichen doch die bisher gewonnenen Erfahrungen schon aus, relativ sichere Prognosen über Hörverbesserungen zu geben. Als Indikationsgebiet für solche Eingriffe gilt die Ankylose des Stapes im ovalen Fensterrahmen, die hauptsächlich durch otosklerotische Veränderungen in diesem Bereich entsteht. Die teilweise oder vollständige Fixierung des Steigbügels führt zu einer zunehmenden Einschränkung des Hörvermögens. Die guten funktionellen Ergebnisse nach Stapesoperationen beruhen letztlich auf der Wiederherstellung der Schwingungsfähigkeit der Gehörknöchelchenkette; sie müssen die Resultate nach Fenestration des horizontalen Bogenganges übertreffen, da die Kettenfunktion bei Anlegung der Fenestra nov-ovalis (Lempert) ausgeschaltet bleibt und damit ein Hördefizit von rund 27 dB (Altmann, v. Békésy, Schubert, Schuknecht, Wever, Wullstein u. a.) unvermeidbar ist.

Die Technik der Steigbügeloperation zeigt eine schrittweise Entwicklung. 1952 empfahl Rosen die indirekte Mobilisierung des Stapes durch dosierte Rüttelbewegungen an seinem Köpfchen. Bald lehrte die Erfahrung, daß die zarten Steigbügelschenkel häufig dem instrumentellen Druck nicht standhalten und brechen, ehe noch die Lösung einer stärkeren Fußplattenankylose gelingt. Auch bei Verwendung von Mikrovibratoren (Frenckner, Goodhill, H. P. House) trat der erwünschte Erfolg nicht immer ein. Der operative Angriffspunkt wurde deshalb später an die fixierte Fußplatte selbst verlegt, woraus die verschiedenen Methoden der direkten Mobilisierung entstanden.

Nach Durchbrechen oder Abmeißeln der Otosklerose-Herde in der Fußplatte (Cawthorne, Derlacki, Dworacek, Goodhill, Heermann, Meurmann, Portmann u. a.) konnte die Beweglichkeit des Steigbügels nun viel häufiger erreicht werden. Der Prozentsatz der Hörverbesserungen stieg damit zwar sprunghaft an, leider waren die Resultate aber häufig nicht von langer Dauer, da durch das Fortbestehen des otosklerotischen Prozesses eine Re-Ankylose nicht verhindert werden konnte (Boenninghaus, Fleischer, Holmgren, Hürzeler, Kos u. Mitarbeiter, Zangemeister, Zöllner u. a.). Mittels der Crurotomia anterior versuchten Fowler und Zöllner deshalb den Otoskleroseherd zu umgehen und erreichten die Schalltransmission in das Innenohr allein über den hinteren, noch beweglichen Fußplattenanteil. Um der möglichen Rezidivgefahr aber noch sicherer zu begegnen, entschloß man sich schließlich, die pathologisch veränderte und im ovalen Fensterrahmen fixierte Fußplatte gänzlich zu entfernen und sie durch ein anderes körpereigenes Gewebe zu ersetzen. Auf dieser nun schwingungsfähigen Ersatz-Fußplatte wird die Mittelohrkette wieder aufgebaut. Als Material für dieses Interpositionsverfahren (Portmann) wird entweder ein Stückchen Venenwand (Shea, Plester, Portmann u. Claverie, Rüedi), ein Bindegewebsläppchen (Zangemeister, Schubert, Schuknecht), Perichondrium (Juers) oder

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Gelfoam (H. P. House) verwendet. Nach experimentellen Untersuchungen von Falk u. Musebeck eignet sich straffes Bindegewebe als Transplantat ganz besonders, weil es wenig Neigung zu Umbauvorgangen zeigt.

Auf Grund einer mehrjahrigen operativen Erfahrung sieht die „Klinik Novotny“, an der fast ausschließlich Bindegewebe als Fußplattenersatz verwendet wird, diese Ansicht auch praktisch bestätigt. Wenngleich in 10% der Fälle postoperativ mit einem Mißerfolg gerechnet werden muß (Novotny), lassen die ubrigen erfolgreich operierten Patienten, deren Zahl um 90% liegt (Glaninger u. Hechl, Schwetz) Re-Ankylosen auch bei Spätkontrollen vermissen.

So sehr durch die Platinektomie auch die Aussicht auf Dauererfolge gestiegen ist (Altmann, Basek u. Hough), durfen die dadurch entstehenden Gefahrenmomente nicht unterschatzt werden. Durch die Entfernung der Steigbugelfußplatte und durch die damit erfolgte Eröffnung des Vestibulum labyrinthi können neben einer Blutung ins Labyrinth (Becker, Boenninghaus, Heermann, Novotny, Shambough) zwei weitere Komplikationsmöglichkeiten das Innenohr gefährden:

1. Ein operativ gesetztes Labyrinthtrauma und
2. Eine Labyrinthinfektion.

ad 1. Um Labyrinthtraumen durch Mittelohroperationen zu vermeiden, wird immer wieder empfohlen, in den Fensterbereichen instrumentell so schonend wie möglich vorzugehen (Brock, Franz, Fraser, Glaninger, Konopacki, Schwetz, Zollner). In erhohtem Maße muß dieses Gebot fur die Manipulationen bei Entfernung der ankylosierten Fußplatte gelten. Trotz Zuhilfenahme des Mikroskopes ist das Vestibulum labyrinthi dabei stets der Gefahr einer mechanischen Irritation ausgesetzt, liegen seine Sinnesendstellen doch nur wenig weit vom Fußplattenniveau entfernt (Anson, Anson u. Bast, Zöllner). Vor allem können mobilisierte Fußplattenanteile, wenn sie im Vestibulum „versinken“ und nicht mehr zu entfernen sind, zu starken vestibulären Irritationen mit nachfolgender Horverschlechterung (Glaninger) oder gar Taubheit (Beickert) fuhren. Selbst die zu starke Invagination eines Bindegewebsläppchens in das Vestibulum verursacht schon heftige vestibuläre Sensationen (Boenninghaus). Falle, bei denen trotz Verschwindens der ganzen Fußplatte in den Labyrinthvorhof weder Störungen im Gleichgewichts- noch im Hörorgan auftreten (Becker), sind deshalb wohl als Ausnahmen zu werten. Auch Becker glaubt, daß dann die Fußplatte in einen solchen Teil des Perilymphraumes gelangt ist, den wir als stumme Zone im Hinblick auf die Fortleitung des Schalles im Innenohr und auf die physiologische Perilymphströmung bezeichnen können. Uns blieb ein so glucklicher Ausgang bei einem einschlägigen Fall leider versagt, hier fuhrte die im Vestibulum verbliebene Fußplatte rasch zur Ertaubung.

Wegen einer fortgeschrittenen Otosklerose wird die 50jährige Patienten Sch. M., die seit 30 Jahren an beiderseitiger Schwerhorigkeit leidet, am 5. Juli 1960 einer

Steigbügeloperation rechts unterzogen. Dabei findet sich die ovale Fensternische durch otosklerotische Wülste stark eingeengt. Die extrem verdickte Fußplatte wird ausgemeißelt und fällt nach ihrer Mobilisierung ins Vestibulum. Wegen starker vestibulärer Reizerscheinungen bei der Patientin müssen die Extraktionsversuche schließlich aufgegeben werden, die Fußplatte wird zur Bogenganggegend hin verlagert und das ovale Fenster mit einem Bindegewebsläppchen, das mit dem Proc. lenticularis incudis in Verbindung gebracht wird, verschlossen. Unter starkem Schwindelgefühl, Spontannystagmus und Brechreiz tritt knapp postoperativ die Ertaubung ein.

Nach den eigenen Beobachtungen ist das Innenohr auch dann einer starken Gefährdung ausgesetzt, wenn eine otosklerotisch verformte Fußplatte nach der Mobilisierung das ovale Fenster wie ein Kugelventil von vestibulär her verschließt. Die Extraktionsversuche an der auf der Perilymphe schwimmenden Fußplatte führen bei nicht vollnarkotisiertem Patienten zu starkem Schwindel und Erbrechen und lassen sich meist erst nach operativer Erweiterung des ovalen Fensters (Heermann) erfolgreich beenden. Eingedenk dieser technischen Schwierigkeiten bei mancher Fußplattenentfernung wäre die Annahme naheliegend, dass die Fensterungsoperation am horizontalen Bogengang (Holmgren, Jenkins, Lempert, Shambough, Sourdille) das Innenohr viel weniger erregt. Während die Eröffnung des Innenohres bei der Stapesplastik durch den otosklerotischen Herd erfolgt, kann die Bogengangsfistel stets im Bereich des normalen Labyrinthknochens und damit fast immer unter den gleichen anatomischen Bedingungen angelegt werden. Man sollte also erwarten, daß das Labyrinth auf das Abheben eines dünnen Knochendeckels über dem horizontalen Bogengang weniger heftig reagiert als auf das Ausbrechen oder Ausmeißeln verdickter Fußplattenteile aus dem ovalen Fenster. Umso erstaunlicher ist die Tatsache, daß die postoperativen vestibulären Reizerscheinungen wie Schwindel, Brechreiz und Nystagmus nach Stapesplastiken seltener und geringer sind als nach der klassischen Fensteroperation (Boenninghaus, Lindner, Heermann, Portmann, Schubert, Schwetz, Wullstein, Zangemeister).

Ad 2. Während die Gefahr einer mechanischen Alteration des Innenohres bei den Steigbügeloperationen fast möchte man sagen in der Hand des Operateurs liegt und damit unter Kontrolle steht, ist nach Entfernung der Fußplatte das eröffnete Vestibulum einer Gefährdung ausgesetzt, die von Haus aus nicht auszuschließen ist und die deshalb keineswegs unterschätzt werden darf: Der Möglichkeit einer *Infektion* vom Mittelohr her.

Wann und wodurch kann eine solche tympanogene Innenohrinfektion bei Stapesplastiken nun erfolgen?

A) Dem zeitlichen Geschehen nach kann *während* der Operation selbst eine Keimverschleppung in das Innenohr stattfinden, sei es durch die Manipulationen bei der Fußplattenentfernung, sei es durch das Einbringen des Interpositionsmaterials in die ovale Fensternische. Voraussetzung

hiefür waren entzündliche Veränderungen im Mittelohr. Dazu muß kurz auf die Indikationsstellung zu den Steigbügeloperationen eingegangen werden. Seit der Wiederaufnahme (siehe unten) dieser Operationen durch Rosen wurden sie vorerst nur bei Vorliegen einer *otosklerotischen* Steigbügelfixation durchgeführt. Selbstverständlich fanden sich dabei stets blande Mittelohrverhältnisse, wie sie eben zum klinischen Bild der Otosklerose gehören. Wenige Jahre später empfahlen Altmann, Zangemeister und Zöllner, die Steigbügelmobilisation auch in jenen Fällen von Adhäsivprozessen vorzunehmen, bei denen die Entzündungsvorgänge im Mittelohr eine Steigbügelankylose verursacht haben. Die *eigene* Erfahrung hat inzwischen an Hand zahlreicher einschlägiger Operationsfällen gelehrt, daß Fußplattenankylosen mit blanden Trommelfellverhältnissen nicht selten sind, bei denen wir otosklerotische Herde vermissen und bei denen es den Anschein hat, als sei die Fußplatte in ihrem Ringbandbereich durch Residuen abgelaufener Entzündungen fixiert. Ob es sich dabei mehr um Ringbandsklerosen oder um Ringbandverknöcherungen (Schubert) handelt, werden die derzeit laufenden Untersuchungen an zahlreichen in vivo entnommenen Fußplatten histologisch klären. Bekanntlich werden diese Fälle einstweilen als „klinische Otosklerose" (Lempert, Müller, Weichselbaumer u. a.) aufgefaßt. Finden sich bei ihnen im Mittelohr auch keine akut entzündlichen Erscheinungen, so ist das Innenohr durch die teilweise oder komplette Eröffnung des ovalen Fensters doch immer einer gewissen Gefahr der Keimeinschleppung ausgesetzt. Der antibiotischen Abschirmung kommt zu diesem Zeitpunkt zweifellos eine eminente Bedeutung zur Verhütung einer Labyrinthitis zu. Trotz dieser sicher sehr effektiven Schutzmaßnahme konnten wir uns aber bis heute nicht entschließen, wie Schubert, eine Vestibulotomie auch bei chronischen Otitiden mit Polypen- und Granulationsbildungen in der Pauke durchzuführen. Dieser Eingriff scheint uns unter solchen Bedingungen wegen der Gefahr einer entzündlichen Propagation in das Innenohr als zu gewagt. Auch im Zeitalter der Antibiotika sollte nicht vergessen werden, daß die Steigbügelchirurgie am Beginn vor allem deshalb in Mißkredit kam, weil diese Operationen häufig in chronisch entzündeten Mittelohrräumen ausgeführt wurden.

Nach entsprechenden Tierversuchen hat Kessel im Jahre 1877[1] zum ersten Mal eine Steigbügelextraktion am Menschen vorgenommen. Trotz der wechselnden Erfolge wurde daraufhin mehrfach der Versuch unternommen, durch Entfernung des fixierten Steigbügels einen Hörgewinn zu erzielen. Überraschend mag heute die Empfehlung des damaligen Schrifttums scheinen, diesen Eingriff eher bei chronischer Mittelohrentzündung als bei Otosklerose vorzunehmen. Beim näheren Studium der Literatur jener Zeit läßt sich die Abneigung, Otosklerosen operativ anzugehen (Blake, Burnett, Grunert, Jack, Vulpius) leicht verstehen. Sie ist vor allem auf zwei Ursachen zurückzuführen.

[1] Die Originalarbeiten befinden sich im Besitz der Klinik.

1. Unter den damaligen technischen Voraussetzungen stieß man bei der Entfernung von Fußplatten, die durch Otoskleroseherde knöchern fixiert waren, oft auf unüberwindbare Schwierigkeiten. Grunert warnte sogar vor Extraktionsversuchen bei Fällen mit sogenannter „innerer Ankylose“. Er versteht darunter jene Veränderungen, bei denen sich der otosklerotische Prozeß hauptsächlich auf der vestibulären Seite der Fußplatte ausdehnt. Wenn wir auch heute imstande sind, solche Situationen durch Erweiterung des ovalen Fensterrahmens (Heermann) operativ zu beherrschen, können wir die Ansicht Grunerts im Hinblick auf die damaligen Operationsbedingungen (kein Operationsmikroskop etc.) durchaus verstehen.

2. Selbst nach gelungener Entfernung eines otosklerotisch fixierten Steigbügels befriedigte das postoperative Hörergebnis häufig nicht. Das ist heute auch begreiflich, da man nach Überwindung der Stapesankylose unter Verzicht auf die notwendige Schalleitung noch nicht versuchte, die Gehörknöchelchenkette im Mittelohr wieder aufzubauen. Dieser Tatsache voll bewußt, resigniert Grunert: „Durch Entfernung des ankylosierten Steigbügels wird ja sowieso die Gehörknöchelchenkette unterbrochen, auf deren physiologische Leistung für die Schalleitung wir somit von vornherein bei der Stapesextraktion verzichten.“

Selbstverständlich war die Stapesextraktion dann leichter auszuführen, wenn der Steigbügel nur durch Bindegewebs- oder Narbenstränge, also Residuen früherer Mittelohreiterungen, fixiert war; aus diesem Grunde liegen darüber auch zahlreiche Berichte vor. Ihnen zufolge zeitigte die Steigbügelextraktion bei Stapesankylosen otitischen Ursprungs gelegentlich auch bessere funktionelle Hörresultate als bei Otosklerose. Trotzdem war die Zahl der erzielten Hörverbesserungen im Vergleich zu den Versagern relativ klein (Dench, Faraci, Garnault, Kessel, Panse, Schwartze, Vulpius) und die Prognose im Einzelfall völlig ungewiß. Als aber durch das Operieren im entzündlichen Milieu auch noch Komplikationen seitens des Labyrinthes mit Ertaubungen zu verzeichnen waren (Bezold, Schwartze), wurde diese Operationsmethode von der Mehrzahl der Autoren als zu gefährlich betrachtet und wieder verlassen. Murdnich resümiert über diese Ära der Steigbügeloperationen: „... dürfte es bei den Eingriffen am ovalen Fenster öfter zu fatalen Zwischenfällen gekommen sein, die wahrscheinlich nicht immer publiziert worden sind. Siebenmann (1900) hätte sonst wohl kaum jeglichen Steigbügeleingriff so energisch abgelehnt.“

Die vorsichtigere Indikationsstellung zur Steigbügeloperation und die Möglichkeit, durch hochdosierte Antibiotika präventive Schutzmaßnahmen für das eröffnete Labyrinth zu ergreifen, sind wohl die Hauptgründe dafür, daß das Innenohr heute kaum mehr einer solchen Gefährdung ausgesetzt ist.

B. Als eine unter Umständen gefährliche Infektionsquelle für das Labyrinth erweist sich das *postoperative* Auftreten einer *akuten* Entzündung im Mittelohr. Selbstverständlich wird die Gefährdung des Vestibulum labyrinthi dann umso größer sein, wenn das interponierte Transplantat das

ovale Fenster nicht komplett verschließt Aus den tierexperimentellen Untersuchungen von Falk und Müsebeck sowie aus den eigenen experimentellen Beobachtungen (s u) geht weiters hervor, daß auch Steigbügelfragmente an einem solchen inkompletten Fensterverschluß Schuld sein können Eine Otitis media acuta kann entweder 1 sofort nach der Operation oder 2 zu einem wesentlich späteren Zeitpunkt entstehen

ad 1 Postoperative Frühschäden Auf Grund der eigenen und der Erfahrung anderer Autoren (Altmann, Aubry, Kinney, Tieffenberg) müssen wir trotz Anwendung von Antibiotika feststellen, daß eine Mittelohraffektion postoperativ nicht immer verhindert werden kann Sie kann rhinogenen oder auch operationstraumatischen Ursprungs sein Altmann beobachtete einen Fall, bei dem ein postoperativ aufgetretener Schnupfen eine eitrige Labyrinthitis mit vollständigem Verlust der Labyrinthfunktion verursachte Möglicherweise kann ein Teil der von anderen Autoren mitgeteilten schweren postoperativen Labyrinthschäden (Heermann, Shea, Martin und Cajgfinger, Fleischer, Weichselbaumer u a) ähnlicher Genese sein Ein eigener Fall zeigt (siehe weiter unten), daß eine entzündliche Mittelohraffektion auch ohne klinische Zeichen einer Otitis media (Trommelfellbefund etc) nach Stapesplastik einen Labyrinthtod verursachen kann Daß es trotz dieser Gefährdung bei den Steigbügelplastiken doch relativ selten zur Labyrinthitis kommt, ist sicherlich auf den antibiotischen Schutz und auf das Interpositionsgewebe, das eine Infektionsbarriere gegen das Innenohr darstellt, zurückzuführen Interessanterweise vermag sich das Vestibulum, wie die Steigbügelextraktion am Tier zeigt (Kessel, Cornelli), durch Neubildung einer Membran, die das offene Fenster schließt, selbst zu schützen Nach neueren Untersuchungen von Bellucci und Wolff findet man diese Membran schon drei Tage nach dem operativen Eingriff

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Hörverschlechterung mit dröhnendem Rauschen am operierten Ohr. *Aufnahmebefund:* 3gradiger Spontannystagmus nach rechts (Gegenseite), linkes Trommelfell grau, eingezogen, trüb. Linkes Hörorgan taub, ausgeschaltet. Liquor 9/3 Zellen. Wegen dieser Labyrinthitiszeichen Vornahme der membranösen *Labyrinthektomie* nach der Methode von Cawthorne. An der tympanalen Seite des Trommelfells entlang der Gehörknöchelchenkette und besonders in der ovalen Fensternische finden sich polypöse Granulationen, so daß der Steigbügel nicht zu sehen ist. Im Cavum tympani wenig Sekret. Ein kegelförmiges Gebilde, in dem der Stapesrest vermutet wird, wird vom Amboß gelöst und aus dem ovalen Fenster gehoben. Beendigung der Operation nach Zerstörung des häutigen Labyrinthes. Knapp postoperativ deutliche Besserung des Schwindels und Sistieren der objektiven Vestibularissymptome.

Das entnommene Präparat (Abb. 1) wird histologisch aufgearbeitet[1], es zeigt einen von Bindegewebe umhüllten Stapesrest. Einer seiner Schenkel ist zur Gänze erhalten und trägt an seinem Ende noch einen kleinen Fußplattenanteil. Das Bindegewebsläppchen ist von Rundzellen infiltriert, zeigt aber auch frische Nekrosen mit Anhäufungen von Granulozyten. Eine ausgedehnte Nekrose findet sich nahe dem Fußteil des Steigbügels, also gegen das Vestibulum zu gelegen. Dieser Befund spricht für das Vorliegen einer *frischen eitrigen Entzündung*, die vom Mittelohr durch das in das ovale Fenster eingelegte Bindegewebsläppchen Richtung Innenohr vorgedrungen ist. Damit scheint auch histologisch die klinische Annahme bestätigt, daß eine tympanale Infektion selbst 4 Monate nach der Stapesplastik eine schwere Labyrinthitis mit Ertaubung verursachen kann.

Eigene Fragestellung

Soweit es die klinische Beobachtung bisher erlaubt, muß ein Teil der labyrinthären Komplikationen nach Steigbügeloperationen auf *postoperativ entstandene Mittelohrentzündungen* zurückgeführt werden. Man darf annehmen, daß die Intensität einer solchen tympanogenen Labyrinthitis auch weitgehend von der Art des Eingriffes am Steigbügel abhängt, da damit das Ausmaß der operativen Eröffnung des Innenohres im Zusammenhang steht. Während bei Perforationen oder Frakturen der Fußplatte die gesetzte Innenohrfistel relativ klein ist, zeigt sie bei der Stapesplastik nach Entfernung der Fußplatte eine größere Ausdehnung. Gerade dann wird der Abdeckung des ovalen Fensters mit körpereigenem Gewebe eine erhöhte Schutzfunktion für das Innenohr zukommen müssen. So verständlich diese Überlegungen auch scheinen mögen, bleiben uns genauere Kenntnisse auf diesem Gebiet am menschlichen Krankenmaterial in der Regel verwehrt. Die vorliegenden tierexperimentellen Untersuchungen sollten deshalb über die postoperative Infektionsgefährdung des Labyrinthes durch das Mittelohr näheren Aufschluß geben. Dabei war unser Augenmerk nicht allein auf die ovale Fenstergegend, sondern auch auf das Verhalten der runden

[1] Für den histologischen Befund sei Hr. Dozent Dr. C. Fellner, Histolog.-embryolog. Institut d. Universität Wien (Vorstand: Prof. Dr. A. Pischinger) herzlichst gedankt.

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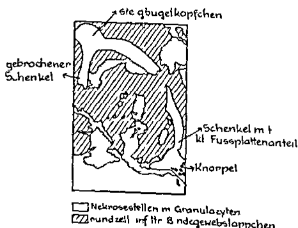


Abb 1 a Abb 1 b

Abb 1 Operationspraparat (Patient W W) und Strichzeichnung 20fache Vergroßerung Stapes im Interpositionsgewebe (Bindegewebe) Tympanale eitrige Infektion Das Bindegewebslappchen bis gegen das Vestibulum zu von frischen Nekrosen (Granulocytenhaufen!) durchsetzt

den Menschen typische embryonalen Knochenstrukturen wie verkalkte Knorpelreste, Globuli ossei knorpelhaltige Interglobularräume Manasse's und lamellenlosen, feinfaserigen Strahnenknochen (Meyer) Ebenso weisen die Gehörknochelchen keine Lamellensysteme auf

Eine größere Anzahl von Versuchstieren wurde Eingriffen unterzogen, die denen ähneln, die am Menschen durchgefuhrt werden Bei 12 Tieren stellte sich trotz antibiotischer Behandlung im postoperativen Stadium spontan eine akute Otitis ein An diesen ließen sich die gestellten Fragen studieren und beantworten

Operationsweg

Die Operationen werden unter sterilen Kautelen in Vollnarkose (intraperitoneale Pentothal Gaben) vorgenommen Nach Abrasieren der Fellhaare im supra und retroauricularen Bereich wird in der Ohrmuschelfalte von oben nach hinten eine bogenformige Incision angelegt Vertiefung der Incision bis zum außeren Gehorgang und Abklappung der Ohrmuschel nach unten Dadurch kommt die obere Circumferenz des Gehörgangschlauches zur Ansicht Er wird vom knochernen Gehörgangsdach bis an das Niveau des Anulus tympanicus mit stumpfen Instrumenten losgelöst Über seiner obersten Kuppe erfolgt ein Einschnitt von innen nach außen



Abb. 2. Operativer Zugangsweg zum ovalen Fenster am Tier. 3fache Vergrößerung. Nach Abtragung eines Teiles der lateralen Attikwand liegt die eingeführte Operationsnadel auf der Steigbügelfußplatte

und nach Spreizung der Schnittränder kommen das Lumen des äußeren Gehörgangs und das Trommelfell zur Darstellung. Unter Schonung des Trommelfells wird die laterale Attikwand aufgesucht und mit dem Bohrer von ihr soviel entfernt, bis der lange Amboßschenkel und der Steigbügel genügend breit ins Blickfeld gelangen. Dieser Zugangsweg gestattet einen optimalen Aufblick auf die in der schmalen ovalen Fensternische gelegene Steigbügelfußplatte. Mit feinsten Nadeln und Häkchen (siehe Abb. 2) werden unter dem *Operationsmikroskop (Zeiß, 16f Vergrößerung)* die verschiedenen Eingriffe am Stapes durchgeführt. Nach Vornahme dieser Manipulationen erfolgt die Deckung des Defektes der Attikwand mit Weichteilgewebe, es werden der Gehörgangsschlauch adaptiert, die Ohrmuschel rückgeklappt und die Operationswunde mit Klammern geschlossen. Die Operationen werden stets nur *einseitig* (rechtes Ohr) vorgenommen, um Vergleichsuntersuchungen mit dem intakten Gegenohr zu ermöglichen.

Der Schwere des Eingriffes entsprechend, treten bei einem Teil der Tiere postoperativ vorübergehend vestibuläre Reizzeichen wie Nystagmus und Fallneigung auf; da diese Untersuchungen die funktionellen Auswirkungen solcher Steigbügeloperationen jedoch nicht zum Inhalt haben, braucht auf sie nicht näher eingegangen werden.

Die Tötung der Versuchstiere erfolgt 2 bis 6 Monate nach dem operativen Eingriff. Fixation in Narkose (intraperitoneale Verabreichung von Pentothal) durch *intravitale Durchspülungsfixation* mit Wittmaack's Fixationsflüssigkeit. Ausspräparation der mittleren Schädelbasis mit beiden Schläfenbeinen. Entkalken und Einbetten in Celloidin. Anfertigung von Serienschnitten (Dicke 18 μ) und *Hämatoxylin-Eosinfärbung*.

Aufgliederung der operativen Eingriffe am Steigbügel:

Tiere	Operationsart	Datum		Überlebenszeit
		der Operation	der Tötung	
1	Stapesplastik (Implantat Bindegewebe)	?	?	2 Monate
2	Stapesplastik (Implantat Bindegewebe)	?	?	?
3	Fußplattenperforation	?	15 xi 1960	5 Monate
4	Frakturierung der Fußplatte	?	?	?
5	Fußplattenperforation (Extraktion u Reposition d Stapes)	?	?	?
6	Brechen beider Stapesschenkel	?	?	?
7	Stapesextraktion (Keine Abdeckung d ovalen Fensters)	?	18 xi 1960	5 Monate
8	Fußplattenperforation und Brechen beider Schenkel	?	17 xi 1960	2½ Monate
9	Stapesextraktion (Keine Abdeckung d ovalen Fensters)	?	17 xi 1960	4 Monate
10	Infrakturierung der Fußplatte Brechen beider Schenkel	?	18 x 1960	6 Monate
11	Extraktion des Stapes (Implantat Bindegewebe)	7 x 1960	22 ii 1961	3½ Monate
12	Fußplattenperforation (Abdeckung mit Bindegewebe)	15 xii 1960	22 ii 1961	2½ Monate

Anmerkung Bei den mit einem Fragezeichen (?) versehenen Angabepunkten können bedauerlicherweis aus folgendem Grund keine präzisen Daten eingesetzt werden Mein Auto wurde im September 1961 nachts in Henndorf (Slbg) aufgebrochen und daraus ein Teil der mitgeführten Schnittserien und der Operationsprotokolle entwendet Die Untersuchungen wurden zwar durch das Vorhandensein von Zweitschnitten später nicht wesentlich beeinträchtigt, der genaue Zeitpunkt der jeweiligen Operation bzw der Tötung der Tiere ließ sich aber in den fraglichen Fällen nicht mehr exakt rekonstruieren Auch bei ihnen betrug die Überlebenszeit aber ausschließlich 2–6 Monate da dieser Zeitplan von Haus aus festgelegt war

Histologische Dokumentation

Tier 1 Serienschnitte Nr 1–71	Tier 8 Serienschnitte Nr 1–40
Tier 2 Serienschnitte Nr 1–39	Tier 9 Serienschnitte Nr 1–73
Tier 3 Serienschnitte Nr 1–63	Tier 10 Serienschnitte Nr 1–28
Tier 4 Serienschnitte Nr 1–41	Tier 11 Serienschnitte Nr 1–43
Tier 5 Serienschnitte Nr 1–99	Tier 12 Serienschnitte Nr 1–49
Tier 6 Serienschnitte Nr 1–49	Gesamtzahl der Schnitte 611
Tier 7 Serienschnitte Nr 1–46	

Untersuchungen

Die Untersuchungen werden in folgender Richtung geführt

A) Der klinischen Beobachtung von Labyrinthitiden nach Steigbügeloperationen entsprechend, gilt das besondere Augenmerk dem Infektionsmodus des Innenohres vom Mittelohr her Dabei scheint die Frage nach

der *Eintrittspforte* der Infektion (rundes oder ovales Fenster), sowie ihr Ausbreitungsweg im Labyrinth selbst von besonderem Interesse.

B) Es wird das Verhalten der *Knochenstruktur der Ossicula* und der Mittelohrwände unter den angeführten Untersuchungsbedingungen studiert, wobei vor allem zu erkennen ist, unter welcher Voraussetzung und in welchem Ausmaß Knochenveränderungen auftreten

C) Schließlich soll festgestellt werden, wie sich das *knöcherne Labyrinth* bei einer operationsbedingten, tympanogenen Labyrinthitis verhält

Ausführungen

A) Die Eintrittspforte und der Ausbreitungsweg der tympanogenen Entzündung in das Innenohr

Bei der gewöhnlichen Otitis media acuta, und nur sie interessiert im Rahmen dieser Fragestellung, erfolgt die tympanogene Labyrinthentzündung beim Menschen in der Regel durch eines der beiden Fenster. Die Infektion verläuft in Form einer Durchwanderung durch die vorerst noch in ihrer Kontinuität erhaltenen Fensterverschlüsse, das sind die Membrana tympani secundaria und das Ringband (Hinsberg) Erst nach Einschmelzung und Zerstörung dieser Gebilde kommt es zum eitrigen Durchbruch in das Innenohr (Zange) Nach Steurer beruht der nekrotische Zerfall der Labyrinthfenster auf Ernährungsstörungen im Labyrinthinneren, die ihrerseits wiederum auf eine intralabyrinthäre Drucksteigerung zurückzuführen sind Größere Statistiken zeigen (Toynbee), daß die banalen Schleimhauteiterungen des Mittelohres relativ selten Anlaß für solche Komplikationen sind Fast sicher tritt eine Labyrinthitis unter diesen Kautelen jedoch dann auf, wenn es im Zuge operativer Manipulationen zu Dislokationen des Steigbügels kommt (Tröltsch, Hinsberg) Selbstverständlich sind das ungewollte Effekte

Bei den in Frage stehenden Otoskleroseoperationen wird das Innenohr im Bereich der Stapesfußplatte dagegen *bewußt* geöffnet Die vorliegenden Untersuchungen sollen daher Aufschluß geben, unter welchen Bedingungen das vestibulotomierte Labyrinth durch eine postoperativ entstandene Mittelohrentzündung gefährdet ist

Tierexperimentelle Beobachtungen liegen darüber nur spärlich vor So warnen Falk und Müsebeck bei Steigbügeloperationen vor nicht entfernten Fußplattenteilen, weil diese den notwendigen Abschluß im Fensterbereich verhindern und damit gefährliche Fistelbildungen verursachen können Nach Schuknecht und Oleksiuk besteht die Gefahr einer purulenten Invasion in das Vestibulum auch dann, wenn die Fußplattenperforation zu breit angelegt ist

Am eigenen Material zeigt sich, daß das Vordringen einer eitrigen Infektion durch das ovale Fenster weitgehend vom Ausmaß der operativen Eröffnung des Innenohres bzw von der Abdeckung der entstandenen Fistel

abhängig ist Ganz massiv verläuft die Labyrinthitis bei den Tieren, bei denen der Steigbügel total entfernt und das ovale Fenster offen belassen wurde (Tiere 7 und 9) Wie erwähnt schließt sich zwar als eine Art „Selbstschutz“ das eröffnete Vestibulum durch Bildung einer Endothelmembran im ovalen Fenster gegen das Mittelohr ab, ihre Schutzfunktion ist aber scheinbar nicht ausreichend, um virulente oder massiv tympanogene Infektionen vom Innenohr abzuwehren (Abb 18) Deckt das, nach der Stapesexhairese eingelegte Bindegewebslappchen dagegen das ovale Fenster vollkommen ab (Tier 11), bleibt das Vestibulum von Entzündungserscheinungen völlig frei Obwohl das Implantat zellig infiltriert ist und in seinem Inneren auch kleinste Nekrosen zeigt, schützt es das Innenohr vor der tympanogenen Infektion Zu gefährlichen Auswirkungen kann es aber kommen wenn der Fensterverschluß mit Bindegewebe nicht exakt gelingt Beim Versuch einer Stapesplastik (Tiere 1 und 2) verhindern zurückgebliebene Steigbügelreste den Abschluß gegen das Innenohr Die daraus resultierenden Innenohrfisteln fuhren in beiden Fällen zu außerordentlich stürmisch verlaufenden Labyrinthitiden Die Abb 3 vermittelt einen solchen Befund Das eingelegte Bindegewebslappchen deckt die ovale Fensternische deshalb nicht zur Gänze ab, weil es daran durch ein eingeklemmtes hinteres Schenkelstück das noch auf einem Fußplattenteilchen aufsitzt, gehindert wird Entlang dieses Schenkelfragments, das sozusagen als „Leitgebilde“ fungiert, erstreckt sich die eitrige Infektion unter den hinteren Fensterrahmen ins Innenohr

Bei Fußplattenperforationen hängt die Gefährdung des Innenohres in der Regel von der Größe des gesetzten Fußplattendefektes ab An kleineren Perforationsstellen bildet sich eine Bindegewebe-Endothel-Membran, die eine genugende Schutzwirkung aufweist, sodaß der Vorhof intakt bleibt (Tier 8) Diese Schutzmembran scheint aber bei großeren Fußplattendefekten eher zu versagen Abb 4 zeigt einen solchen Fall (Tier 3) Die tympanogene Infektion erstreckt sich durch die perforierte Fußplatte in das Vestibulum und fuhrt zu einer fibrinösen Labyrinthitis Wird dagegen ein größerer Fußplattendefekt mit einem kleinen Bindegewebsläppchen verschlossen (Tier 12), bleibt das Vestibulum von einer Entzündung verschont Kommt es bei diesen Manipulationen am Steigbugel zu seiner Dislokation (Tier 5), scheint das Innenohr noch mehr gefährdet Man erkennt in Abb 5 eine relativ kleine Fußplattenperforation Bei der Operation wurde der Stapes extrahiert, anschließend aber sofort wieder in seinen Fensterrahmen eingesetzt Bindegewebe deckt nun nicht nur den Fußplattendefekt sondern verbindet auch die dislozierten Gelenksflachen Durch diese Bindegewebsbrucken kommt es obwohl die Perforationsöffnung an der Fußplatte nicht groß ist zu einer Einwanderung der Entzundung ins Innenohr Diese Bindegewebsbarriere, selbst zellig infiltriert, halt zwar den Eitereinbruch ins Vestibulum auf sie kann hier aber eine fibrinose Exsudatbildung die sich schon bindegewebig organisiert zeigt nicht verhindern

Wurde die Fußplatte nicht perforiert sondern nur frakturiert (Tiere 4



Abb. 3. Tier 2 (Serie, Schnitt 31). 30fache Vergrößerung. Das eingesetzte Bindegewebsläppchen schließt das ovale Fenster nicht komplett ab. Entlang des verbliebenen Schenkelfragmentes des Steigbügels erfolgt der Eitereinbruch in das Innenohr.



Abb. 4. Tier 3 (Serie, Schnitt 38). 30fache Vergrößerung. Ein größerer Fußplattendefekt wurde nicht abgedeckt. Die tympanogene Infektion führt zu einer fibrinösen Labyrinthitis.



Abb 5 Tier 5 (Serie, Schnitt 5) 30fache Vergrößerung kleinere Fußplattenperforation Der Stapes wurde extrahiert und sofort wieder eingesetzt Zeichen einer fibrinosen Labyrinthitis im Vestibulum



Abb 6 Tier 4 (Serie, Schnitt 4) 48fache Vergrößerung Fußplattenfraktur Das Bindegewebe im Bruchspalt unterbindet die Fortleitung der Mittelohrentzundung in das Vestibulum

und 10) bleibt das Innenohr stets intakt. Der knöcherne Defektbezirk ist so klein, daß das den Bruchspalt ausfüllende Bindegewebe die Fortleitung der Mittelohrentzündung in den Vorhof gänzlich zu unterbinden vermag (Abb. 6).

Ein weiteres Interesse gilt dem *Verhalten der Membrana tympani secundaria* unter dem Einfluß einer *akuten* Mittelohrentzündung *nach* Steigbügeloperationen. Steurer konnte im Tierversuch nachweisen, daß artifizielle Entzündungen eher durch das runde als durch das ovale Fenster in das Innenohr einbrechen. Er meint, daß die runde Fenstermembran infolge ihres anatomischen Aufbaues und wegen ihres größeren Flächeninhaltes für die Diffusion von chemischen Substanzen, Keimgiften und Bakterien aus dem Mittelohr ins Labyrinth viel geeigneter scheint als das straffe, verhältnismäßig dicke Ringband des ovalen Fensters. Diese Ansicht scheint durch die Beobachtung erhärtet, daß Tiere mit entzündlichen Mittelohrerkrankungen am *nicht* operierten Gegenohr des öfteren Diffusionslabyrinthitiden durch die *runde* Fenstermembran aufweisen, während das Ringband und das Vestibulum völlig intakt bleiben. *Steurer sieht aber* nach *künstlich* gesetzten Mittelohrentzündungen auch eitrige Durchbrüche durch die Membrana tympani secundaria. Wenn bei den eigenen Versuchstieren ein solcher Eitereinbruch am unoperierten Ohr nicht bemerkt wird, hängt das wohl mit dem Umstand zusammen, daß die traumatische Otitis erfahrungsgemäß stürmischer verläuft als die spontan entstandene. Die in Einzelfällen an operierten Tieren (Tier 4 und 6) in Erscheinung tretende Diffusionslabyrinthitis zeigt sich in Form einer serösen oder serös-fibrinösen Exsudatbildung; sie findet sich in einem meist nur umschriebenen Bereich der basal gelegenen Scala tympani. Eitrige *Durchbrüche* durch die *runde* Fenstermembran werden am eigenen Untersuchungsmaterial vor allem dann beobachtet, wenn sich die Mittelohreiterung auch durch das ovale Fenster ins Innenohr erstreckt (Tiere 1 und 2). Bei diesen frischen Labyrinthitisfällen sind sowohl die Scala vestibuli als auch die Scala tympani ziemlich gleichmäßig von purulentem Exsudat erfüllt. Auch die Vorstellung, daß die Intensität der Infektion mit der Entfernung vom Ort des Durchbruchs abnimmt (Steurer), läßt hier also keinen Rückschluß zu, von welchem Fenster aus die Labyrinthitis ihren Anfang nahm. Im allgemeinen darf trotzdem angenommen werden, daß erst die vom Vestibulum ausgehende Entzündung im Innenohr Wegbereiter für die Destruktion der Membrana secundaria ist. Diese Auffassung korrespondiert mit den Untersuchungen Zanges. Danach beginnt die Zerstörung dieser Membran scheinbar durch Ernährungsstörungen bedingt an ihrer innenohrwärts gelegenen elastischen Faserschicht, während ihre tympanale Schleimhautschicht der Destruktion noch länger Widerstand entgegensetzt.

Auch die Fälle mit ausgeheilter Labyrinthitis (Tiere 3, [illegible] 7 und 9) geben schließlich keinen konkreten Hinweis, welches Fenster der ursprüngliche Einbruchsort der Entzündung war. Die Beantwortung dieser Frage wird hier dadurch erschwert, daß die Organisationsvorgänge in der Schnecke die



Abb. 7. Tier 8 (Serie Schnitt 181) 40fache Vergrößerung. Eiterdurchbruch durch die runde Fenstermembran. Purulentes Exsudat in der Scala tympani, kein pathologisches Sekret in der Scala vestibuli und im Ductus cochlearis.

Fenstergegenden meist mit einbeziehen und so feinere Differenzierungen unmöglich machen.

Wie ein Einzelfall zeigt (Tier 8), kann es aber auch möglicherweise durch die Virulenz der Infektion bedingt, zu einem *isolierten* Durchbruch der Mittelohreiterung durch die *runde* Fenstermembran kommen. Nach der Fußplattenperforation kam es zum bindegewebigen Verschluß des Knochendefektes. Diese Bindegewebsplombe erweist sich als gute Barriere gegen die tympanogene Eiterung, denn das Vestibulum bleibt frei von jeder Entzündung. Dagegen erfolgt vom Mittelohr her der Eitereinbruch durch die runde Fenstermembran (Abb. 7). Im Bilde rechts zeigt sich die Membran rupturiert, die Scala tympani ist von leukozitären Infiltraten erfüllt. Weder in der Scala vestibuli noch im Ductus cochlearis liegt pathologisches Sekret. Aber auch in der Scala tympani findet sich die Eiterung nur im Basalbereich. In ihrer Mittelwindung erkennt man noch etwas zellarmes Exsudat, in der Spitzenwindung ist auch diese Scala entzündungsfrei. Es entsteht also der Eindruck, daß wie in noch milderer Form bei der Diffusionslabyrinthitis auch die eitrige Labyrinthitis, so sie vom runden Fenster ausgeht, keinen besonders stürmischen Verlauf zeigt. Ganz anders, wenn die eitrige Infektion durch das ovale Fenster erfolgt. Die gesamte

Schnecke und die Bogengänge werden dann im selben Maße ergriffen, wobei sich das eitrige Exsudat vor allem in den perilymphatischen Räumen ausbreitet. Mit welcher Intensität dieser Einbruch aber weiter verläuft, zeigt folgender Umstand. Steurer sieht bei seinen Tierversuchen, daß in den perilymphatischen Räumen viel stärkere entzündliche Veränderungen auftreten als in den endolymphatischen, er schreibt: „Während wir im Perilymphraum schon eitrige Exsudatausscheidungen haben, finden wir im Endolymphraum nur leichte hydropische Veränderungen oder mitunter auch keinerlei Reaktion." Dieses Bild scheint jenen Fällen zu entsprechen, bei denen die Infektion vom runden Fenster her kommt. Beim massiven Eitereinbruch durch das ovale Fenster werden aber auch die Schranken des Endolymphschlauches durchbrochen, so daß seine Räume nicht nur im Schnecken- sondern auch im Bogengangsabschnitt (Abb. 8, Tier 2) von leukocytären Infiltraten erfüllt sind.

Die häufig angestellte Beobachtung, daß bei milderen Formen der Labyrinthitis die Schnecke stärker betroffen ist als der Bogengangbereich, kommt beim Tier 3 besonders kraß zum Ausdruck. Nach einer breiten Fußplattenperforation zeigt die entzündlich affizierte Schnecke starke Bindegewebs- und Knochenproliferation. Die peri- und endolymphatischen Hohlräume der Cochlea sind mit Bindegewebe und Knochenneubildungen so ausgefüllt, daß ihre Struktur kaum mehr zu erkennen ist. In den perilymphatischen Räumen der Bogengänge dagegen findet sich als Resultat der Organisationsvorgänge nur ein Netz von zartem Bindegewebe, in dem mehr minder spärlich Rundzellen eingelagert sind. Der Endolymphraum zeigt hier überhaupt keine entzündliche Reaktion. Vor allem springt also die Diskrepanz im Verhalten der Endolymphsysteme beider Innenohrabschnitte ins Auge. Während es im Vestibulum und Bogengangsbereich normale Verhältnisse erkennen läßt, ist der Ductus cochlearis der gesamten Schnecke bindegewebig umgebaut. Die Erklärung für diese stärkere Alteration könnte darin liegen, daß der Ductus cochlearis bei einem „doppelten Fensterdurchbruch" (Steurer) — auch das erwähnte Tier zeigt eine Zerstörung der runden Fenstermembran — durch seine Lage zwischen den beiden Seiten Entzündungen gegenüber besonders exponiert ist.

B) *Die knöchernen Veränderungen im Mittelohr*

Über den Zustand an den Stapes-Bruchstellen nach Steigbügeloperationen beim Menschen, liegen verständlicher Weise nur ganz vereinzelte Beobachtungen vor (Altmann und Waltner, Brunner). Nach diesen Untersuchungen zeigt der Strahnenknochen des Steigbügels ebensowenig Neigung zur knöchernen Kallusbildung, wie der der endochondralen Labyrinthkapsel. Damit scheint die Annahme erlaubt, daß auch die Frakturen des Steigbügels nicht knöchern, sondern nur bindegewebig verheilen. Auf Grund ihrer tierexperimentellen Studien sind Altmann und Basek allerdings der Meinung, daß bei den Versuchstieren die Tendenz zu knöchernen Reparationsvorgänge am Stapes im allgemeinen größer ist als beim Menschen.



Abb. 8. Tier 9 (Serie, Schnitt 31). 190fache Vergrößerung. Leukocytäres Infiltrat im Endolymphraum eines Bogenganges.

Dabei sind die Knochenneubildungen entweder periostalen oder endostalen Ursprungs. Darüber hinaus heben die Autoren hervor, daß dieses Knochenwachstum dann einen besonderen Anreiz erfahrt, wenn sich im Mittelohr entzündliche Affektionen finden. Sie führen diese Beobachtung auf einen stimulierenden Effekt der Infektion auf die osteogenetische Potenz des Periosts und des Endosts zurück. Da die Frakturen an der Fußplatte eher zur Kallusbildung neigen als an den Schenkeln, wird diese Potenz vor allem dem Endost zugesprochen. Nach Singleton und Schuknecht verheilen Schenkelbrüche umso eher knöchern, wenn die Frakturenden nicht weit voneinander liegen. Auch Bellucci und Wolff sehen die Kallusbildung vor allem dort ausgeprägt, wo die Knochenfragmente in situ blieben.

Angeregt durch die tympanoplastischen Operationen und die daraus resultierenden Fragen wurden gerade in jüngster Zeit auch Hammer und Amboß von chronisch entzündeten Mittelohrräumen entnommen einer genauen histologischen Prüfung unterzogen (Gunnel, Grippaudo, Pollock, Walsh *und Mitarbeiter*). *Übereinstimmend werden vor allem im kompak*ten Knochen dieser Ossicula starke Umbauvorgänge unter dem Bild einer Osteomyelitis gefunden. Ähnliche, wenn auch nicht so schwere Veränderungen sieht v. Schulthess aber auch bei Gehörknöchelchen, die aus Mittelohren mit akuter Entzündung stammen. In beiden Fällen überwiegt ein deutlicher Knochenabbau, die Knochenanbauzonen nur äußerst selten zu sehen sind. Das entspricht auch der klinischen Beobachtung, da im entzündlichen Mittelohr sklerotische oder hypertrophische Gehörknöchelchen kaum zu finden sind.

An Hand des eigenen Untersuchungsmaterials zeigt sich nach operativen Eingriffen im *Steigbügel* folgendes: Liegen die Stapesbruchstellen in mit



Abb. 9. Tier 6 (Serie Schnitt 37). 48fache Vergrößerung. Bruchstelle des hinteren Steigbügelschenkels. Die Mittelohrentzündung zeigt noch keine Organisationsvorgänge. Fehlen einer Bindegewebsbrücke zwischen beiden Frakturenden trotz ihrer geringen Dislokation.

eitrigem Exsudat erfüllten Hohlräumen oder steht das exsudative Stadium überhaupt noch im Vordergrund der Entzündung, wird praktisch jede Heilungstendenz vermißt (Abb. 9). Obwohl beide Frakturenden des hinteren Stapesschenkels sehr nahe beisammen liegen, sind sie nicht einmal noch bindegewebig vereinigt. Erst wenn es im späteren Stadium der Otitis zu Organisationsvorgängen wie Einsprossen von Gefäßen und Bindegewebsproliferation kommt, lassen sich Reparationszeichen erkennen, die an einem infrakturierten Steigbügelschenkel (z. B. Abb. 4) schließlich zu knöchernen Kallusbildung führen. Je stärker der Stapes operativ geschädigt wurde, desto stärker ist der periostale Knochenanbau. Durch diese Knochenneubildung erscheinen dann z. B. *die* Fußplatte und der vordere Steigbügelschenkel klobig verdickt (Abb. 10). Entgegen den Beobachtungen von Altmann und Basek muß der Knochenanbau an einer operativ geschädigten Fußplatte aber keineswegs hauptsächlich vom Endost ausgehen. In Abb. 11 handelt es sich um eine Fußplattenperforation, die eine starke *periostale* Knochenneubildung auslöste; sie erstreckt sich von der tympanalen Fußplattenseite *bis in den* frakturierten hinteren Schenkelbereich. Splitter vom ursprünglichen Strähnen [illegible] n sind darin noch gut zu erkennen. Beachtenswert ist das stark [illegible] te vestibulär gelegene Endost (in der



Abb. 10. Tier 8 (Serie, Schnitt 5). 48fache Vergrößerung. Operativ traumatisierter Steigbügel. Die Mittelohrentzündung in Organisation begriffen. Starke Knochenneubildung am vorderen Stapesschenkel und an der Fußplatte.



Abb. 11. Tier 8 (Serie, Schnitt 1). 110fache Vergrößerung. Periostaler Knochenanbau an dem gebrochenen hinteren Stapesschenkel und der perforierten Fußplatte.



Abb. 12. Tier 11 (Serie, Schnitt 34). 48fache Vergrößerung. Amboßkörper im „Umbau". Der ursprüngliche Strähnenknochen wird ersetzt. Im Resorptionsraum links Osteoklasten, um den größeren mehr rechts periostaler Neuknochen.

Abb. 11 rechts), das die Lücke in der Fußplatte verschließt und damit eine Labyrinthinfektion vom Mittelohr her verhindert.

Ist die Otitis media in Organisation begriffen, beobachtet man auch am *Amboß*, auch wenn er selbst nicht verletzt wurde, unter Umständen Zeichen eines starken Knochenumbaues. Dies ist dann der Fall, wenn sich die Gelenksenden des für ein Operationstrauma sehr anfälligen Amboß-Steigbügelgelenks disloziert finden oder wenn das Gelenk zwar intakt, aber krankhaft verändert ist. Im Amboßkörper sieht man dann einen orange gefärbten Neuknochen, der sich in der H.E.-Färbung deutlich vom ursprünglichen Strähnenknochen abhebt. Er baut sich um Resorptionsräume auf, in denen sich vorerst reichlich zellige Elemente finden. Osteoklasten und Osteoblasten zeugen vom stattfindenden Knochenumbau, der von der periostalen Knochenschicht aus beginnt (Abb. 12). In der Abbildung erkennt man das Einwachsen des Neuknochens in den Amboßkörper links unten, während das Zentrum und der rechte Knochenabschnitt noch normalen Strähnenknochen aufweisen. Ein fortgeschrittenes Stadium zeigt die Abb. 13. Bis auf eine Knocheninsel in der Mitte, ist der Strähnenknochen von peripher her durch neu gebildeten Knochen ersetzt. Die in ihm gelegenen relativ großen Resorptionsräume füllt nunmehr fibroblastisches Material.

Unter dem Einfluß von Proliferationsvorgängen im Mittelohr kann auch der *Hammer* dieselben Knochenveränderungen aufweisen. Sie kommen aber nur dann vor, wenn das Hammer-Amboßgelenk nach scheinbar artifizieller Zerreißung bindegewebig ausgefüllt ist (siehe Abb. 13 links) oder wenn der Hammer selbst z. B. durch Abtragung seines Kopfes (Einzelfall,



Abb. 13. Tier 12 (Serie, Schnitt 28). 40fache Vergrößerung. Der fast völlig umgebaute Amboßkörper zeigt nur mehr in der Mitte eine Insel von Strähnenknochen. Die großen Resorptionsräume füllt fibroblastisches Material. Das Hammer-Amboßgelenk (links) bindegewebig durchwachsen und infiltriert.



Abb. 14. Tier 11 (Serie, Schnitt 34). Ausschnitt aus Abb. 12. 190fache Vergrößerung. Periostknospen dringen in den Amboßkörper ein (oben). Im Resorptionsraum links Osteoklasten um den darunter liegenden osteoiden Neuknochen.

Tier 4) operativ traumatisiert wurde. Auffallend ist in diesen Fällen, daß vor allem das Manubrium mallei dann praktisch nurmehr aus Neuknochen besteht. Es scheint also außer Zweifel, daß nicht nur mechanische Läsionen an den Gehörknöchelchen selbst, sondern auch eine Störung an



ABB 15 Tier 7 (Serie, Schnitt 3) 300fache Vergrößerung Amboß Resorptionsraum mit Osteoklasten und Osteoblasten Osteoide Knochenneubildung (dunkler gefärbt)

ihren Gelenken das periostale Knochenwachstum aktivieren Ob dafür ursächlich lokale Faktoren oder rein nutritive Momente verantwortlich sind, entzieht sich derzeit leider unserer Kenntnis Wie beim Menschen (Anson), fehlt uns ja auch bei den Versuchstieren ein ausreichendes Wissen über die Gefäßernährung der Gehörknöchelchenkette, obwohl angenommen werden darf, daß gerade ihr eine wesentliche Bedeutung für knöcherne Umbauvorgänge zukommt Eine Erklärung für dieses merkwürdige Phänomen ist somit weder auf Grund des Literaturstudiums, noch nach eingehender Besprechung mit Pathologen zu geben

Der feingewebliche Ablauf des Knochenumbaues läßt sich am relativ großen Amboßkörper besonders gut verfolgen Wie Abb 14 zeigt, dringen Periostknospen von peripher in den toten Knochen ein, dessen Zellkerne nicht mehr färbbar sind Von zellhältigen Resorptionsräumen aus bauen Osteoklasten den Strähnenknochen ab (links im Bild) An seine Stelle tritt orange gefärbtes (H E-Färbung) osteoides Knochengewebe (im Bild unten) das schließlich den ursprünglichen Knochen mehr und mehr ersetzt In stärkerer Vergrößerung zeigt ein solcher Resorptionsraum (Abb 15) neben Osteoklasten einen im Aufbau befindlichen Neuknochen (in Bildmitte dunkler gefärbt) mit reichlicher Anlagerung von Osteoblasten

Die *knöchernen Wände* der Paukenhöhle zeigen sich bei Mittelohrentzündungen in der Regel nur wenig verändert Unter dem durch dichtes Bindegewebe und Rundzelleninfiltrate oft stark verdickten Periost liegen höchstens schmale, orange gefärbte angebaute periostale Knochensäume Stärkere Knochenneubildungen treten auch hier erst dann auf, wenn die Mittelohrwandung operativ geschädigt wurde Nach Entnahme eines Stück-



Abb. 16a. Tier 5 (Serie Schnitt 21). 48fache Vergrößerung. Tympanale Wand des knöchernen Facialiskanales. Über dem Nerven verschließt periostaler Neuknochen die operativ gesetzte Knochenlücke



Abb. 16b. Tier 5 (Serie Schnitt 21, vergrößerter Bildausschnitt aus Abb. 16a). 150fache Vergrößerung. Über dem Nerven links noch eine Schicht intakten Strähnenknochens. Die Knochenlücke (rechts) schließt Appositionsknochen

chens vom Knochenkanal des Mittelohranteiles des Nervus facialis z. B., schließt sich die Knochenlücke unter den Zeichen eines stürmischen Knochenumbaues (Abb. 16a). Im vergrößerten Bildausschnitt (Abb. 16b) erkennt man unten den Nerv, darüber rechts findet sich die Stelle des gesetzten Knochendefektes, nun von appositionell entstandenem Neu-



Abb. 19. Tier 7 (Serie Schnitt 3). 120fache Vergrößerung. Endostaler Neuknochen umwuchert haubenförmig den Knorpelbesatz des ovalen Fensterrahmens.



Abb. 20. Tier 9 (Serie Schnitt 50). Ausschnitt aus Abb. 18). 120fache Vergrößerung. Endostaler Neuknochen ersetzt teilweise den Strähnenknochen der Labyrinthkapsel (vorderer ovaler Fensterrahmen).

zum Bild der bindegewebigen Obliteration (Abb. 17, Tier 9). Auf Grund dieser vehementen Bindegewebsreaktion erfolgt auch meist eine stärkere Knochenneubildung, die in der Cochlea und besonders deutlich im Vestibulum in Erscheinung tritt (Abb. 18, Tier 9). Vom Vorhof aus kann sich das endostale Knochengewebe auch über den ovalen Fensterrahmen, seinen noch erhaltenen Knorpelbesatz haubenförmig umgebend (Abb. 19, Tier 7),



Abb. 21. Tier 9 (Serie Schnitt 21). 190fache Vergrößerung. Weite Periostknospen dringen von tympanal gegen die enchondrale Schicht der Labyrinthkapsel.

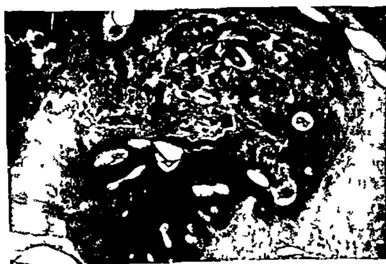


Abb. 2 . Tier (Serie Schnitt 3). 40fache Vergrößerung. Der Strahlenknochen der Labyrinthkapsel wird durch neugebildete endo- und periostale Knochenzüge durchsetzt. Das endostale Knochenwachstum überwiegt.

bis gegen das Mittelohr hin erstrecken. Schließlich verursacht dieses Knochenwachstum aber nicht nur Anbau, sondern auch Umbauvorgänge in der Labyrinthkapsel selbst. Abb. 20 (Tier 9) zeigt einen vergrößerten Bildausschnitt von Abb. 18. Man erkennt, daß der endostale Neuknochen auch auf die enchondrale Schicht des vorderen ovalen Fensterrahmens übergreift und dort den Strähnenknochen teilweise ersetzt hat. Während solche Knochenveränderungen in den übrigen Abschnitten der Labyrinthkapsel

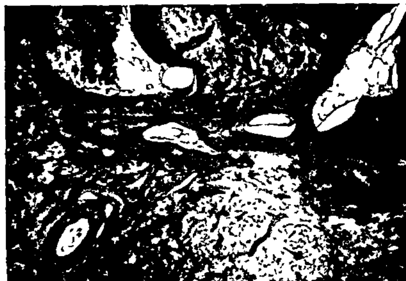


Abb. 23. Tier 7 (Serie, Schnitt 19). 30fache Vergrößerung. Starke endostale Knochenneubildung im Bereich des horizontalen und des unteren Bogenganges.

nur bei einer entsprechenden Intensität des *endostalen* Knochenwachstums zu vermerken sind, unterliegt die laterale, also tympanal gelegene Kapselwand auch Einflüssen, die vom *Periost* des Mittelohres entstammen. Durch die Mittelohrentzündung bedingt, dringen, zahlreicher und tiefer als das unter normalen Umständen der Fall ist (Eckert-Möbius), weite Periostknospen gegen die enchondrale Knochenschicht vor (Abb. 21, Tier 9); sie verursachen dort einen Knochenumbau dergestalt, daß der Strähnenknochen nun auch in seinen äußeren, periostnahen Lagen von orangefarbenen neugebildeten Knochenzügen durchsetzt erscheint. Die mittlere Labyrinthkapselschicht erweckt nun den Eindruck, als sei der Altknochen durch den in Abb. 22 (Tier 7) dunkler gefärbten Neuknochen direkt „zerfressen". Trotzdem ist aber aus der Abbildung deutlich zu ersehen, daß die Knochenneubildung vom Endost her auch in diesen Fällen stets dominiert.

Da sich die Ausbreitung der Labyrinthitis in der Regel im Bogengangbereich nicht so heftig manifestiert wie in dem der Schnecke, sind die Bindegewebsproliferationen der Ausheilungsphase dort nicht so stark ausgeprägt. Das scheint aber auch der Grund dafür, daß in den Bogengängen nur ein einziges Mal (Tier 7) endostale Knochenwucherungen im perilymphatischen Raum beobachtet wurden. In Abb. 23 (Tier 7) wird unter dem quer getroffenen Musculus stapedius das Lumen des horizontalen und des unteren Bogenganges durch die manschettenförmige Anordnung der endostalen Knochenwucherungen stark eingeengt. Durch diese Knochenzeichnung heben sich die beiden Bogengänge vom umgebenden Strähnenknochen besonders deutlich ab.

Neben einer endostalen Knochenneubildung in den Labyrinthhohlräumen

kann es also auch in der enchondralen Schicht der Labyrinthkapsel zu Umbauvorgängen kommen Morphologisch betrachtet unterliegt der Strähnenknochen dort den selben Veränderungen wie der Strähnenknochen der Gehörknöchelchen Zum Unterschied vom Mittelohr ist der Neuknochen im Innenohr allerdings nicht periostalen, sondern hauptsächlich endostalen Ursprungs Nur die gegen das Mittelohr zu gelegene Kapselwand zeigt unter Umständen ein Einwachsen periostalen Knochens, wodurch aber ein noch starkerer Abbau und Ersatz des Strähnenknochens ausgelöst wird Trotz heftigster Eiterungen im Mittel- und Innenohr kam es bei keinem unserer Tiere zu einer Knochennekrose mit Sequesterbildungen an der Labyrinthkapsel, wie dies von Steurer beschrieben wird Der Kontur der Kapsel blieb auch bei starkem Knochenumbau stets intakt und ist gegen die übrige Labyrinthstruktur immer gut abgrenzbar

ZUSAMMENFASSUNG

Wie auch Steurer meint wird der Wert von Tierversuchen vor allem dadurch bestimmt, daß sich die gewonnenen Ergebnisse auch auf die menschliche Pathologie übertragen lassen. Es darf berechtigter Weise angenommen werden, daß die von uns experimentell gesetzten Operationseffekte am Steigbügel auch bei Stapesoperationen am Menschen vorkommen und zu erwarten sind. Was die Infektionsgefährdung des Innenohres allerdings betrifft, sollen Versuchstiere z. B. nach Fensterungsoperationen gegen Labyrinthitiden anfälliger sein als der Mensch (Takami). Dieser Umstand ist vielleicht mit ein Grund, daß die kasuistische Zahl von Labyrinthkomplikationen nach operativer Eröffnung des Innenohres relativ klein ist. Ein weiterer Grund mag aber auch darin liegen, daß im allgemeinen wenig Neigung besteht, Komplikationen zu publizieren. Unter diesem Aspekt muß den vorliegenden Ergebnissen doch ein gewisser praktischer Wert für die Otochirurgie zugesprochen werden, da sie einen Einblick in postoperative Vorgänge im Mittel- und Innenohr bringen, deren Studium uns am menschlichen Schläfenbein zum Glück meist versagt bleibt.

Das Resultat dieser Untersuchungen sei in seinen wichtigsten Punkten schlagwortartig wiederholt.

1. Eine massive Einwanderung der Mittelohreiterung ins Labyrinth beobachtet man dann, wenn das ovale Fenster nach Entfernung des Steigbügels offen bleibt, oder wenn trotz des Versuches, es abzudecken (Bindegewebsimplantat), nur ein inkompletter Fensterverschluß erreicht wird.

2. Die im ovalen Fenster als eine Art „Selbstschutz" sich bildende Bindegewebsmembran schützt das Innenohr bei breit angelegten Fußplattenperforationen nur relativ. Sie kann die Entstehung einer serösen oder serösfibrinösen Labyrinthitis nicht verhindern.

3. Wird nach Steigbügelentfernung oder ausgedehntem Fußplattendefekt mittels Implantat ein kompletter Fensterverschluß erzielt, kommt es im Vestibulum zu keinen Entzündungszeichen. Das eingelegte Bindegewebe erweist sich somit als ausgezeichnete Infektionsbarriere.

4. Bei Fußplattenfrakturen, bei denen die knöchernen Defektbezirke ja relativ klein sind, vermag das Bindegewebe, das den Bruchspalt ausfüllt, die Fortleitung der Mittelohrentzündung ins Innenohr gänzlich zu unterbinden.

5. Erfolgt der Einbruch durch das ovale Fenster, werden Schnecke und Bogengangssystem stark befallen. Die Infektion verläuft auffallend heftig und durchbricht unter Umständen auch die Schranken des Endolymphschlauches.

6 Kommt es vom ovalen Fenster her zu einer milderen Form der Labyrinthitis (seros oder seros fibrinos) zeigt die Schnecke eine stärkere Anfälligkeit gegen die Entzündung als das Bogengangssystem Diese Erscheinung wird als Auswirkung des doppelten Fensterdurchbruchs gedeutet

7 Das runde Fenster zeigt eine stärkere Durchlässigkeit für tympanogene Infektionen ins Innenohr als das ovale Die von hier ausgehenden Entzündungen ob Fensterdiffusionslabyrinthitis oder isolierter Eiterdurchbruch durch die runde Fenstermembran nehmen aber intralabyrinthär keinen stürmischen Verlauf

8 Unter gewissen Bedingungen kommt es zu einer starken Knochenneubildung an den Ossicula Voraussetzung dafür ist a) ein *mechanischer* Reiz (operative Schädigung der Gehörknöchelchen oder ihrer Gelenke) und b) ein *biologischer* Reiz (Aktivierung des Stoffwechsels durch die Mittelohrentzündung)

9 Diese Knochenneubildungen sind besonders nach Stapesfrakturen stark ausgeprägt und führen u U durch ihr exophytisches Wachstum zu Deformitäten an den Steigbügelfragmenten Sie nehmen gegen die Fußplatte hin zu Der Neuknochen ist *periostalen* Ursprungs *Endostales* Knochenwachstum an der vestibulären Seite der Fußplatte wird in verstärktem Ausmaß nur bei bindegewebigen Organisationsvorgängen im Vestibulum also nach Labyrinthitiden beobachtet

10 Ein starker Knochenumbau zeigt sich an Hammer und Amboß Oft werden große Teile des Strahnenknochens durch *periostalen* Neuknochen ersetzt Die grobe Konfiguration dieser Ossicula bleibt dabei aber unverändert

11 An den Mittelohrwänden beobachtet man erst nach einer operativen Schädigung stärkere Knochenappositionen

12 Das Bindegewebe das bei der Ausheilung einer Labyrinthitis in Erscheinung tritt neigt auf Grund seiner endostalen Abstammung zu starker Verknöcherung In den Labyrinthhohlräumen mehr im Schnecken als im Bogengangabschnitt kommt es zum *Anbau endostalen* Knochens In der Labyrinthkapsel wird der Strähnenknochen zum Teil durch diesen Neuknochen ersetzt Der *Knochenumbau* ist im Bereich der lateral gelegenen Kapselwand besonders deutlich wenn von tympanal her auch ein *periostales* Knochenwachstum zu erkennen ist

SUMMARY

This research, which is based on animal experimentation, primarily concerns itself with probing the question of middle ear infections, resulting from penetration into the inner ear through stapes surgery Labyrinth complications which have been clinically observed after stapes surgery, and also the trend toward performing vestibulotomies despite infected middle ears, have shown the importance of this research Additionally, reactions of the operatively traumatized ossicular chain were studied under otitic conditions The resultant modification of bone structure appears to be of interest with regards to tympanoplastic surgery In conclusion, further experimentation was performed to determine the extent of reaction which the bony system of the inner ear manifests after postoperative tympanogene infections

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SUPPLEMENTUM [illegible]

ELECTRON MICROSCOPIC AND ELECTROPHYSIOLOGICAL STUDIES ON THE LATERAL LINE CANAL ORGAN

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ACTA OTO-LARYNGOLOGICA

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SUPPLEMENTUM 199

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ÅKE FLOCK

STOCKHOLM 1965

CONTENTS

The Ultrastructure of the Lateral Line Canal Organ

INTRODUCTION

The lateral line organs are developed from the acustico lateralis placode which gives rise also to the sensory organs of the labyrinth. The common origin of these organs in reflected not only by their similarity in structure but also, as it appears, by the common principles of their receptor mechanisms. Because of its accessibility and relatively simple structure the lateral line canal organ may serve as a suitable model for studies of the basic principles of sensory perception in the acustico lateralis organs. The understanding of the function of the lateral line organ is dependent on a thorough knowledge of its structure, a fact which has prompted the present investigation.

MATERIAL AND METHODS

This investigation was carried out on the supra temporal lateral line canal organs, mainly the third one, and on the first few organs of the body canal (Figs. 1, 2) of the teleost fish (burbot) *Lota vulgaris*, a member of the (cod) *Gadus* family. An incision was made into the supra orbital canal, and the body canal was cut through a few centimeters behind the gillcover. The fixation fluid could then be perfused through the canal with the aid of a pipette before the sensory areas were dissected out. In other cases the appropriate organ was exposed by dissection in order to keep the cupula intact before the fixation fluid was applied.

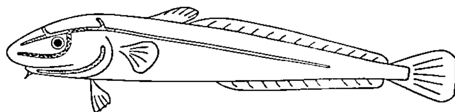


Fig. 1. Schematic drawing illustrating the distribution of the lateral line canal system of *Lota vulgaris*.

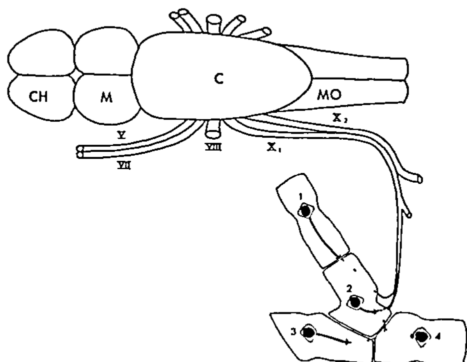


Fig. 2. Diagram showing the location of the four supra-temporal organs (1–4) within their bony capsules and their innervation and topographical relationship to the brain. Dorsal view. *CH* cerebral hemisphere, *M* metencephalon, *C* cerebellum, *MO*, medulla oblongata, *V*, N. trigeminus, *VII*, N. facialis, *VIII*, N. statoacusticus, X_1, lateralis branch of N. vagus, X_2, N. vagus.

The anatomy and the innervation of the organs were studied by dissection in the fresh and in the fixed state.

Specimens for routine histology were fixed in 10% formaldehyde or Bouin's solution, embedded in paraffine, sectioned, mounted and stained with haematoxylin eosine, Weigert's iron-haematoxylin-thiazinrot-picric acid or Mallory's connective tissue stain.

Specimens for light and electron microscopy were fixed for 3 hours in cold 1 per cent osmium tetroxide solution buffered with veronal acetate (Rhodin, 1954), dehydrated in alcohol and embedded in Epon (Luft, 1961). For phase contrast microscopy 1-μ-thick sections were cut with glass knives on an LKB Ultrotome, collected from 10 per cent alcohol and mounted in Epon on objective slides. For ordinary light microscopy similar sections were stained with toluidine blue (Richardson *et al.*, 1960). For electron microscopy grey or white sections were collected on 100 mesh copper grids and stained with 1.2 per cent uranyl acetate in 10 per cent alcohol for 1 hour at 60°C (Brody, 1959).

Electron microscopy was performed with a Siemens Elmiskop I. A Zeiss photo microscope was used for the light microscopical study. The nerve fibre calibre analysis was made on photographs of toluidine blue stained sections prepared according to the methods described above.

RESULTS

General Structure

The lateral line organs are present in all primarily aquatic vertebrates, i e cyclostomes fishes and amphibia The organs are distributed in rows on the head and along the body of the animal The most primitive form, the epidermal lateral line organ, is situated within the epidermis with the cupula projecting out into the surrounding water The epidermal organ has alternatively been called by different authors free organ, pit organ or superficial or epidermal neuromast In cyclostomes, aquatic amphibia and in some fishes no further development is seen, but in other fishes a number of sensory areas become more highly differentiated and are sunk down into furrows in the skin which ultimately close into canals (Dijkgraaf, 1952) However, epidermal organs are generally still present along the canals In this paper the terms lateral line canal organ and lateral line epidermal organ will be used respectively for each sensory area of the two different types, while the term lateral line system designates the entire set of sensory organs belonging to both types

The lateral line canals comprise on the head a supra orbital, an infra-

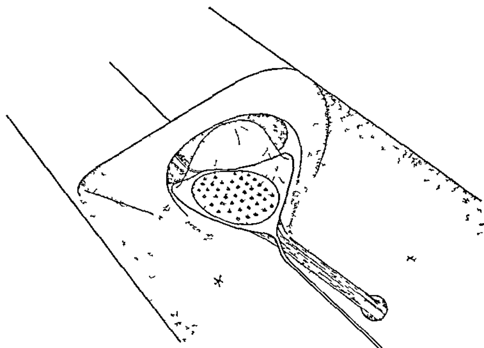


FIG 3 Schematic drawing showing the general structure of the third supra temporal lateral line canal organ For a description see the text

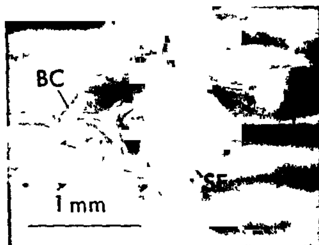


Fig. 4. Lateral line canal organ exposed by dissection and stained with osmium tetroxide. The sensory epithelium (*SE*) rests upon an oval disc formed by the branching nerve fibres of the innervating nerve (*N*). The mantle cells zone (*M*) extends somewhat up the walls of the canal. Note the strangulation of the canal at the level of the sensory area. *BC*, blood capillary. × 27.

orbital, a supra-temporal and a hyo-mandibular canal, and on the trunk a main body canal (Fig. 1). Many sensory areas are present within each canal and in *Lota vulgaris* the sensory areas appear with an interval of 5–10 mm. The supra-temporal canal comprises 4 organs, the body canal about 25 organs. The present investigation has been carried out on the supra-temporal organs, mainly the third one (Fig. 2), and on the few first organs of the trunk, to which the following description applies.

At the level of each organ the wall of the canal is reinforced by an osseous half-cylinder, which is cartilaginous towards each end where it articulates with its neighbours (Fig. 2). The third supra-temporal organ is joined by connective tissue to the bone of the skull.

The general structure of the sensory organ is diagrammatically represented in Fig. 3. The sensory area rests upon a saddle shaped hillock of loose connective tissue, situated in the middle of the ossicle (Figs. 3, 4). The nerve and the blood vessels enter through a hole in the bone at the bottom of the canal. Reaching the hillock, the nerve and the blood vessels spread into a dense network, forming a stiff oval disc upon which the sensory epithelium rests. Specialized supporting cells, the mantle cells, build up a peripheral zone, which gets somewhat broader up the walls of the canal. Towards the middle of the canal the mantle cell zone is drawn out into a thin chord, the connecting chord, passing to the next organ. The gelatinous cupula rests upon the sensory epithelium covering also the mantle cell zone. The cupula almost fills the canal, the top reaching the roof, which is lowered by a ridge of loose connective tissue (Fig. 3). Consequently, the cross section of the canal is smaller at the level of the organ than elsewhere.

In *Lota vulgaris* the system of canals communicates with the exterior only through one rostral and one caudal pore (Hyrtl, 1866) while in other fishes there is usually one pore at each organ

Fine Structure and Innervation of the Sensory Epithelium

Sensory cells

The flask-shaped sensory cells or hair cells are about 40 μ long and 10 μ wide They are interposed between surrounding supporting cells, to which they are joined by desmosomes, and reach half way down the sensory epithelium (Figs 5 6, 7) From a cuticular plate in the top of each hair cell a bundle of sensory hairs protrudes into the overlying cupula Several nerve endings make contact with the bottom of the cell

The oval nucleus is located in the middle of the cell and occupies a large

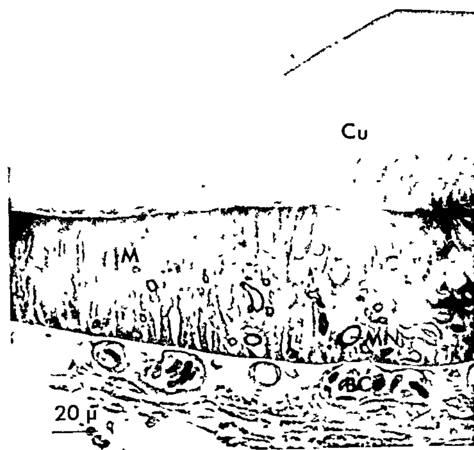


Fig 5 The gelatinous cupula (*Cu*) covers not only the region of hair cells (*HC*) but also the mantle cell zone (*M*) Below the sensory epithelium blood capillaries (*BC*) form an extensive network *MN* Myelinated nerve fibre Tholuidine blue stained Epon section × 640

FIG. 6. Schematic drawing showing the ultrastructure of the sensory epithelium of the lateral line canal organ of *Lota vulgaris*.

area of the cross section of the cell at this level. It is surrounded by a nuclear membrane, which is rather wrinkled and often forms deep recesses into the apical part of the nucleus. The karyoplasm is pale in comparison with that of mammalian vestibular hair cells (Wersäll, 1956).

Vesicles with a diameter of 300–400 Å are especially abundant in the lower half of the cell, and throughout the cytoplasm larger vesicles, 400 to 1,500 Å in diameter, are also seen (Fig. 32). Mitochondria measuring 0.5–3 μ are frequent in the supranuclear part and in the synaptic area. At the level



FIG 7 Survey picture of the sensory epithelium The hair cells (*HC*) are provided with sensory hairs (*SH*) and reach half way down the sensory epithelium which rests upon a basement membrane (*BM*) They are surrounded by supporting cells (*SC*) and are innervated by the nerve endings (*NE*) of myelinated (*MN*) and unmyelinated (*UN*) nerve fibres *BC*, Blood capillary × 1,700

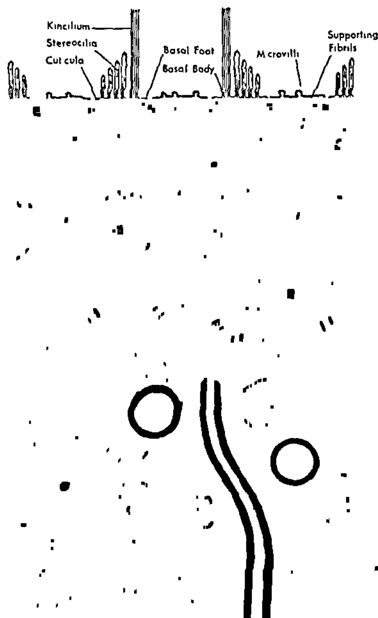


Fig 6 Schematic drawing showing the ultrastructure of the sensory epithelium of the lateral line canal organ of *Lota vulgaris*

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Fig. 8. Cross section through a sensory hair bundle showing the regular arrangement of the stereocilia (*St*) and the peripheral position of the kinocilium (*K*). Note the fibrillar network interwoven between the stereocilia. × 53 000

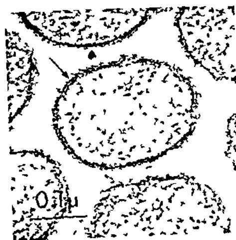


Fig. 9. The core of each stereocilium is fibrillar and is surrounded by a triple layered plasma membrane (arrow). × 150 000

of the nucleus long and slender mitochondria are oriented parallel to the axis of the cell The endoplasmatic reticulum is represented below the nucleus by alpha-cytomembranes lined with ribosomes Free aggregates of ribosomes are also frequent, especially in the supranuclear region No regular infranuclear membrane system, such as described in mammalian vestibular Type I hair cells (Wersäll, 1956), is found Branching tubules, with a diameter of 300–700 Å, lined with granules about 50 Å in diameter, are present throughout the cell It is possible to determine the extension of this tubular system only by three dimensional reconstructions from serial sections Above the nucleus, osmophilic tubular filaments, which are 150–200 Å wide and may reach a length of 2 5 μ, run from the cuticular region downwards into the cell (Fig 33) The apical ends of such tubules can sometimes be seen to contact the cuticular plate, but never has any continuity or contact been observed between them and the rootlets of the stereocilia These tubules apparently do not branch and they are distinct from the thin bundles of supporting fibrils which are at times seen to travel through the cytoplasm emanating mainly from desmosomes which are present at the apical circumference and along the sides of the cell

Multivesicular bodies and inclusion bodies are present above the nucleus, and in this region smooth membranes surrounding flat spaces form a somewhat irregular Golgi apparatus

Sensory hair bundle and cuticle

Organization of the sensory hair bundle The bundle of sensory hairs protruding from the top of each hair cell is composed of 40–50 stereocilia and one kinocilium which is located in the periphery of the bundle (Fig 8) In cross sections through the bundle, where the organization of the sensory hairs can be accurately studied, it is seen that the stereocilia are arranged in 7 parallel rows, each consisting of 5 or 6 stereocilia, lined up behind the kinocilium, towards which the central row points In relation to the central row each peripheral row is successively advanced towards the kinocilium in such a way that a V-shaped indentation is formed, opening at an angle of 110°–115° towards the kinocilium (Fig 8) In the two outer rows the first stereocilium is generally missing An eighth or a ninth row of short stereocilia is sometimes present at either side of the bundle This organization of the sensory hair bundle is consistent throughout the sensory epithelium and no other types of bundles have been encountered

Stereocilia The length of the stereocilia increases stepwise towards the kinocilium, their length ranging from 0 5–5 μ Each stereocilium is composed of a fibrillar protoplasmic core surrounded by a triple layered plasma membrane which forms a tube with a diameter of about 0 15 μ (Fig 9), and which is drawn out into a tip at the peripheral end of the stereocilium (Fig 10) The stereocilium tapers down to a minimum diameter of 0 1 μ before penetrating into the cell (Figs 11, 12) From a level of 0 2 μ above

FIG. 8. Cross section through a sensory hair bundle showing the regular arrangement of the stereocilia (*St*) and the peripheral position of the kinocilium (*K*). Note the fibrillar network interwoven between the stereocilia. × 53 000

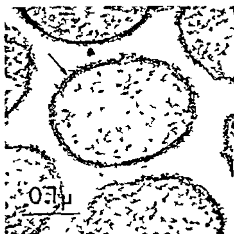


FIG. 9. The core of each stereocilium is fibrillar and is surrounded by a triple layered plasma membrane (arrow). × 150 000



Fig 10 At the distal end of the stereocilium the plasma membrane is drawn out into a tip × 120 000

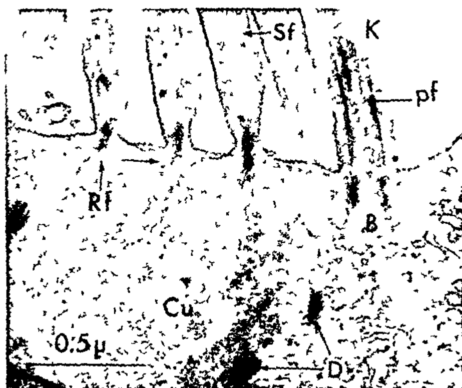


Fig 11 Towards the cell surface the stereocillar fibrils (Sf) gather into a dense core which again resolves into rootlet fibrils (Rf) which penetrate into the cuticular plate (u) Short radiating strands project from the rootlet fibrils (arrow) Dense bodies (D) are seen at the interface between the cuticle and the cytoplasm The peripheral filaments pf of the kinocilium (K) are continuous with the walls of the basal body (B) which is located in an area devoid of cuticular substance × 58 000



FIG 12 The rootlets (*R*) of the stereocilia are lodged within the cuticle in rootlet canals (*RC*), the walls of which appear condensed (*C*) × 90 000

the cell surface a network of thin strands, 100 Å wide, is seen between the stereocilia (Figs 8, 11, 12)

The bulk of the stereocilium contains about 75 fibrils measuring 30–40 Å (Figs 9, 11) Towards the base of the cilium these fibrils unite into a dense axial fibre which again resolves into fibrils which penetrate into the cuticular plate (Figs 11, 12) About 20 fibrils with a diameter of 50–100 Å make up each rootlet which is lodged in 1 5 μ wide canals in the cuticule (Fig 13) The rootlet fibrils spread in a conical fashion on their course downwards, and the space between them and the wall of the cuticular canal thus continually decreases before they end about 0 4 μ beneath the cell surface Within each rootlet an interior light lumen is seen Thin osmophilic strands measuring 25–50 Å extend radiating from the rootlet fibrils towards the cuticle across the light space of the rootlet canal, the walls of which appear condensed where the radiating strands end (Figs 11, 12, 13) The structure of the stereocilium is diagrammatically represented in Fig 14

Kinocilium The kinocilium shows a typical arrangement of nine peripheral double barrelled filaments surrounding a central pair of simple filaments (Fig 8) It is surrounded by a plasma membrane forming a tube with a diameter of about 0 25 μ–0 3 μ While the two central filaments end 0 3 μ above the cell surface the peripheral filaments are continuous with the filaments of the basal body, which is located in the periphery of the cell in an area devoid of cuticular substance (Figs 11, 15) Fig 14 shows a

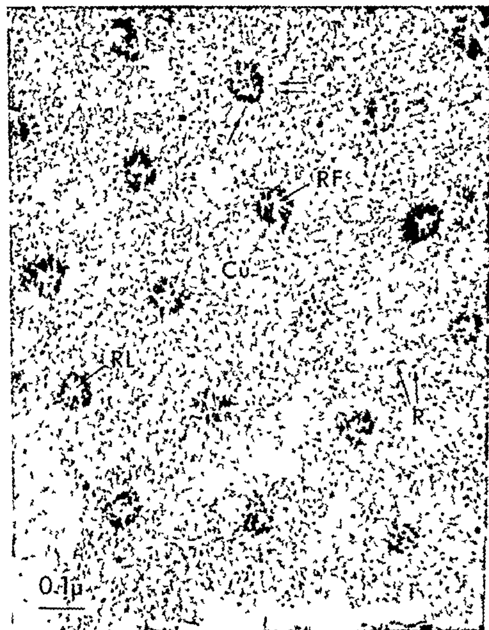


Fig 13 Cross section through the rootlets of the stereocilia Each rootlet is composed by a number of fibrils (*RF*) surrounding a lumen (*RL*) Radiating osmophilic strands (arrows) traverse the rootlet canal Short rods (*R*) can be distinguished in the granular cuticular substance (*Cu*) × 110 000

diagrammatic reconstruction of the kinocilium and its basal body as well as of the stereocilium The circle of peripheral filaments has a diameter of 0 18 μ each peripheral filament measures 200 Å point 350 Å Each central filament has a diameter of 200 Å and their centres are located 300 Å apart A line connecting the two central filaments is perpendicular to the rows of stereocilia and it is the unpaired peripheral filament No 1 (num

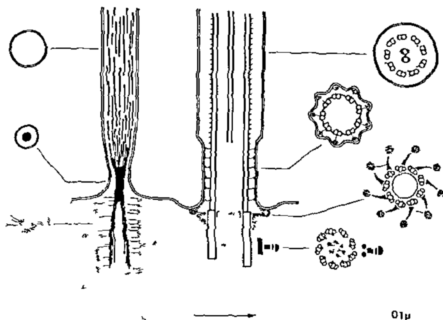


Fig. 14. Schematic drawing showing the ultrastructure of the stereocilium with its rootlet and the kinocilium and its basal body. The arrow indicates the direction of excitatory stimulation. For a description see the text.

bered clockwise according to Afzelius 1959) that faces the stereocilia. Three short arms project from each peripheral filament, two of them *point in a* clockwise direction (when looking from inside the cell) whereas the *third* one points radially towards the plasma membrane. A thin strand of osmiophilic substance which is condensed in the middle of the strand converges from each peripheral filament towards the central filaments. The strands *running to the filaments 5, 6 and 1 are generally the most distinct ones*. The space between the central filaments is occupied by an *opaque substance*. Sometimes vesicles measuring about 300 Å are present between the peripheral filaments and the plasma membrane.

The two central filaments end 0.3 μ above the cell surface (Fig. 11). At this level the components of the kinocilium and its plasma membrane undergo a rearrangement leading to the formation of the neck of the kinocilium. In the neck region nine shallow grooves which run parallel to the axis of the cilium impinge upon the plasma membrane between each of *the peripheral filaments*. The circumference of the kinocilium *therefore* assumes a wavy appearance. The radially pointing arm of each peripheral filament is more distinct and now extends closer to the plasma membrane where it contacts a chord of osmiophilic substance which occupies each groove formed at the inner side of the plasma membrane opposite to each peripheral filament. Neighbouring peripheral filaments are interconnected



Fig. 15. The basal body (*B*) of the kinocilium is located in an area devoid of cuticular substance. This pole of the cell contains an abundance of vesicles. Between the cuticular plate (*Cu*) and the cell membrane supporting fibrils (*SF*), vesicles and ribosomes (*R*) are seen. × 19 000.



Fig 16



Fig 17

Fig 16 Cross section through the basal body just beneath the cell surface From each of the nine triplicate tubules (*T*) a spoke of osmophilic substance (*S*) extends × 148 000

Fig 17 Cross section through the basal body at a slightly deeper level than in Fig 16 × 128 000



Fig 18 Longitudinal section through the basal body showing the basal foot (*BF*) which projects from it away from the stereocilia × 84 000

by arms which extend from that part of subfibre A which faces clockwise and peripherally, and meet the middle of subfibre B of the neighbouring filament

On passing into the cell the peripheral filaments are transformed into triplicate tubules making up the wall of the basal body (Figs 11, 14, 16) The basal body is a short cylinder, 0 2 μ long and 0 18 μ wide At the level just beneath the surface of the cell nine spokes of osmophilic material extend like the paddles of a shovel-wheel in a clockwise direction from the

triplicate tubules obliquely up towards the plasma membrane at the base of the kinocilium (Figs 14, 16). Where the tips of these spokes reach the cell membrane they contact globular condensations which represent the lower aspects of the chords, running in the grooves of the neck region At this level a diffuse basal plate is seen within the lumen of the basal body Further down the spokes are shortened and a dense strand appears along the inner margin of each triplicate tubule (Figs 14, 17) At the lower end of the basal body a granular plate or vesicular material is often present (Fig 11)

A club-like basal foot ending with a peripheral swelling invariably projects from the wall of the basal body at a location corresponding to the peripheral filaments 5 and 6, that is away from the stereocilia (Figs 14, 18) At its base two short bars run along the wall of the basal body The shaft and the peripheral swelling appears to be composed by piled-up plates as is indicated by its laminated structure

Cuticle The cuticle, which is about 1 μ deep, occupies the top of the hair cell apart from an area in one pole of the cell where the kinocilium is situated (Fig. 15) The cuticle does not quite reach the plasma membrane at the walls of the hair cell top but leaves a circumferential space, 0 2–0 4 μ wide, containing vesicles, ribosomes and supporting fibrils which have a tangential course and run parallel to the cell surface The granular cuticular substance appears homogeneous but in high magnification pictures of thin sections aggregates of osmophilic rods which are 200–300 Å long and 25–50 Å broad can be distinguished (Fig 15) At the interface between the cuticular plate and the apical cytoplasm of the hair cell densely staining bodies are frequently present (Fig 11)

Orientation of the sensory cells

The sensory cells are morphologically polarized and by observing the position of the kinocilium in the sensory hair bundle in sections cut parallel to the surface of the sensory epithelium it is possible to determine the orientation of each cell in the phase contrast or in the electron microscope (Fig 19). It is found that over the entire sensory epithelium two groups of hair cells can be distinguished according to their different orientation Adjacent hair cells are oriented with their kinocilia pointing in opposite directions towards the head or towards the tail alternatively All hair cells are oriented parallel to the axis of the canal with a maximal deviation from this orientation of 10°–15° Cells with opposing orientation are often grouped in pairs of two with their kinocilia facing each other

Innervation

Nerve fibres The lateral line organs on the head are innervated by a complex nerve trunk, contributed to by N trigeminus V and N facialis VII, and those of the body by the lateralis branch of N vagus X A ganglion is



Fig. 19 Adjacent hair cells are oriented with their kinocilia pointing in opposite directions towards the head or towards the tail alternatively but always along the axis of the lateral line canal × 10 000

found both at the anterior and at the posterior roots just before they enter medulla oblongata at the two sides of N statoacusticus, to which they are closely apposed (Fig. 2). A more thorough description is given by Cole (1898). Each nerve innervating an organ contains 100–125 myelinated nerve fibres with a diameter ranging from 1 to 25 μ, though fibres above 21 μ in

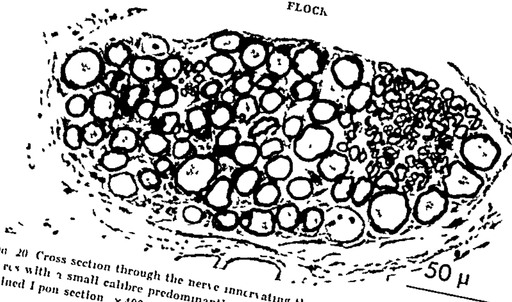
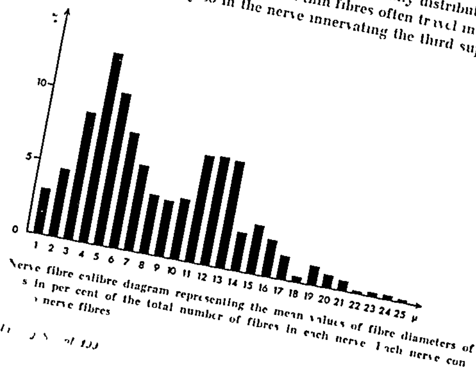


Fig 20 Cross section through the nerve innervating the third supratemporal organ Nerve fibres with a small calibre predominantly travel in one side of the nerve Toluidine blue stained Epon section ×400

diameter are only rarely encountered Two groups of fibres can be distinguished having an average diameter of 4 μ and 12 μ respectively (Figs 20, 21, 22) The calibre diagram of Fig 21 represents the mean values of nerve fibre diameters in eight nerves Large nerves of big animals contain the same number of fibres and exhibit the same calibre diagram but the nerve fibres lie more scattered and are separated from each other by a loose connective tissue The two groups of fibres are randomly distributed to the sensory epithelium, but in the nerve stem thin fibres often travel in separate bundles and conspicuously so in the nerve innervating the third supra-tem-



Nerve fibre calibre diagram representing the mean values of fibre diameters of
s in per cent of the total number of fibres in each nerve Each nerve con
nerve fibres

of 133

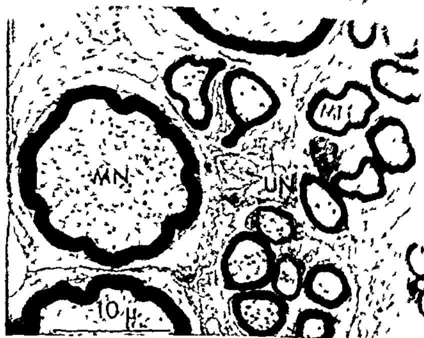


FIG 22 The nerve innervating an organ contains large and small myelinated fibres (MN) and unmyelinated ones (UN) × 3 000

poral organ, where the thin fibres are often confined to the dorsal part of the nerve (Fig 20)

The electron microscope reveals the existence also of thin unmyelinated fibres with a diameter of 0 3 to 1 5 μ (Figs 22 23) They are accompanied by Schwann cells which may enclose one or several fibres It has not been possible to determine their destination Unmyelinated fibres are seen in

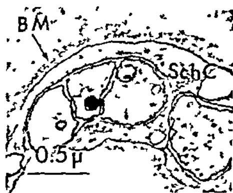


FIG 23 Many unmyelinated nerve fibres are generally ensheathed by the same Schwann cell (SchC) which is separated from the connective tissue by a thin basement membrane (BM) × 32 000



Fig. 24. An unmyelinated nerve fibre (UN) is seen to enter the sensory epithelium. The endoplasmatic reticulum of the supporting cells (SC) is heavily distended. SchC Schwann cell. × 11 000

break through the basal membrane of the sensory epithelium (Fig. 24) but it is not known whether these fibres represent the unmyelinated fibres of the nerve stem or are derived from myelinated ones.

The nerve is surrounded by a perineurium of connective tissue containing fibroblasts and collagen fibrils. Within the nerve fibroblasts partly surround groups of fibres and between them bundles of collagen fibrils are seen to travel in different directions (Fig. 22). The Schwann cells surrounding the nerve fibres, myelinated as well as unmyelinated, are separated by a thin basal membrane from the connective tissue of the nerve (Fig. 21).

The myelinated nerve fibres exhibit the structure common to peripheral nerves. The axoplasm contains neurofilaments, mitochondria, vesicles and tubules. At the internal and external foldings of the Schwann cell, the dense lamellae of the myelin sheath is formed by the fusion of the plasma membranes of consecutive layers.

In teleost fishes the myelin sheath is generally retained for a distance even within the sensory epithelium (Figs. 5, 7) while in other animals the myelin sheath is lost when the fibres penetrate the basal membrane. Inside the sensory epithelium the myelinated nerve fibres are ensheathed by sur-



FIG 25 Within the sensory epithelium the Schwann cell (*SchC*), surrounding a myelinated nerve fibre is separated from a neighbouring supporting cell (SC) by a dense intercellular space (arrow) *Ax* Axon *NF*, neurofilaments, *My*, myelin sheath, *C* cisterna of endoplasmatic reticulum, *R* ribosomes × 110 000

rounding supporting cells, which are separated from the plasma membrane of the Schwann cell by a 300–400 Å wide intercellular space which appears to be rather dense (Fig 25) Both inside and outside the epithelium typical nodes of Ranvier are recognized where the nerve fibres branch Beneath the innervated hair cell the myelin sheath is shed by successive unfolding of the myelin lamellae (Fig 26) and the axon continues its course for a short distance surrounded only by the supporting cells before it reaches the bottom of the hair cell where the nerve endings are developed Naked axons ensheathed only by supporting cells may also be seen to travel for longer distances beneath the sensory cells

Since there are more hair cells within the sensory epithelium than there are nerve fibres in the innervating nerve stem each nerve fibre innervates many hair cells The convergence is more than 10 hair cells per nerve fibre

Nerve endings Each hair cell is innervated by several nerve endings which make contact with the bottom of the cell Two types of endings can be distinguished, which are termed non-granulated and granulated

The *non-granulated nerve endings* are often seen to derive from myelinated nerve fibres (Fig 26) They contain scattered neurofilaments, mitochondria, tubules and vesicles with a diameter ranging from 200 to 2,000 Å, some of which contain a dense granular or a vesicular core (Figs



Fig. [illegible]. Non granulated nerve endings (*NE*) often derive from myelinated nerve fibres and may impinge upon the bottom of the hair cell (*HC*). The myelin sheath (*My*) is shed by successive unfolding of the myelin lamellae. *SB* Synaptic bar. ×24 000

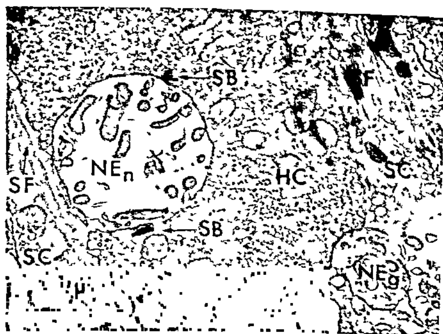


Fig 27 While a non granulated nerve ending (NE_n) deeply invaginates the hair cell (*HC*) only a shallow impression is seen where a granulated nerve ending (NE_g) is apposed to it *SB* Synaptic bar, *SC* supporting cell *SF*, supporting fibrils × 27 000

26–29) Large endings of this type are located in invaginations at the hair cell or they may contact the bottom sides of the cell only slightly impinging it (Fig 28) Also, small endings indent the haid cell wall higher up the sides of the cell (Fig 31) At each of these synapses one or more dense synaptic bars are found inside the hair cell separated by about 600 Å from the hair cell membrane The synaptic bar is surrounded by a cluster of vesicles with a diameter of about 350 Å, which are lined along its sides and are also found between the synaptic bar and the synaptic membrane (Figs 29, 30) At the synaptic bar the synaptic membranes of the hair cell and the nerve ending follow a wavy but parallel course and in each of about five valleys, which appear at a period of about 1,000 Å, dense ovoid bodies 500 Å long are located The triple layered synaptic membranes are separated from each other by a 150–200 Å wide synaptic cleft Within the synaptic cleft a faint line of osmophilic substance follows the synaptic membrane of the nerve ending at a distance of about 30 Å (Fig 30) Intra-synaptic filaments bridge the synaptic space at an interval of 100–200 Å Inside the nerve ending osmophilic substance is aggregated along the synaptic membrane which therefore appears more heavily stained than the synaptic membrane of the hair cell Inside the hair cell an accessory double membrane is in a few cases seen to cover partly the region of contact with a non granulated nerve ending (Fig 28) Such double membranes are some-

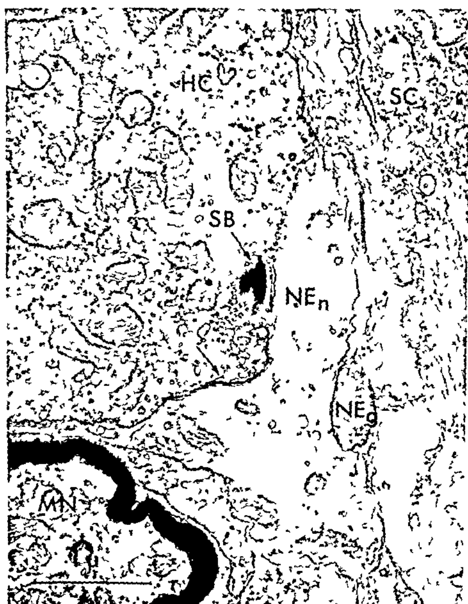


Fig. 28. A non-granulated nerve ending (NE_n) innervating a hair cell (*HC*) is in its turn contacted by a granulated nerve ending (NE_g). *SB* Synaptic bar, *SC* supporting cell, *MN* myelinated nerve fibre. Arrow indicates accessory double membrane. × 29 000.

times also seen without association to nerve endings along the hair cell bottom.

The *granulated nerve endings*, which are generally smaller than the non-granulated ones, are located in shallow impressions at the bottom of the hair cells (Figs. 27, 31) or they may sometimes contact the outside of a large non-granulated nerve ending (Fig. 28). The granulated nerve endings contain an abundance of vesicles, 300–400 Å in diameter, which are as a rule evenly distributed throughout the nerve ending, but which are some-



Fig 29 Inside the hair cell (*HC*) a synaptic bar (*SB*) is seen at the region of synaptic contact with a non granulated nerve ending (NE_a) V, Vesicles, *T*, tubule, *SC*, supporting cell ×46 000

times concentrated to the region of synaptic contact with the hair cell Larger vesicles, some of which contain a dense granule, short tubules and mitochondria may also be seen Inside the hair cell an accessory double membrane is generally seen running along the synaptic membranes at a distance of about 75 Å from it (Figs 31, 32) Dense granules which are about 150 Å in diameter and have the appearance of ribosomes, are often seen associated to that side of the double membrane which faces towards the hair cell cytoplasm The synaptic membranes are separated by a 150–200 Å wide synaptic cleft, which is partly bridged by intrasynaptic filaments At those points where vesicles of the granulated nerve endings lie close to the synaptic membrane, the membrane often bulges towards the vesicle (Fig 32) Sometimes one or a few vesicles occupy the synaptic cleft which is then widened At such points the adjacent accessory membrane is usually interrupted or resolving (Fig 32)

Supporting cells

The hair cells are encased by supporting cells, some of [illegible]h may probably reach from the basement membrane to the surfac[illegible] the epithelium,

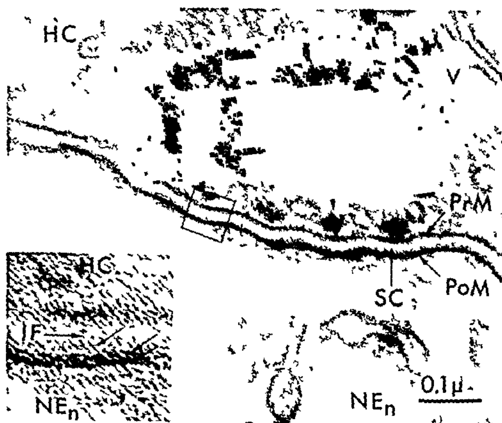


FIG. 30. At the synaptic bar (SB) the synaptic area exhibits an elaborate ultrastructu
HC hair cell NE non-granulated nerve ending PrM presynaptic membrane P
postsynaptic membrane SC synaptic cleft V vesicles DB dense body Insert
intrasynaptic filament single arrow osmiophilic line following postsynaptic membra
double arrows the two dense lines of the unit membrane ×1 0 000

while others do not reach beyond the bottoms of the hair cells. Each supporting cell is equipped with an ovoid nucleus which is situated at differe levels but always below the sensory cells. At their apical circumferenc neighbouring cells exhibit the complex junctional features commonly se at epithelial surfaces (Farquhar and Palade 1963): a zona occludens, desmosomes and interdigitating interfaces (Fig. 33). The cytoplasm is traversed by bundles of supporting fibrils which are most numerous in t apical part of the cell and which mainly emanate from the desmosom (Fig. 34).

The basal part of the supporting cell is occupied by an extensive end plasmatic reticulum (Figs. 24, 25). The alpha cytomembranes are oft heavily distended by a sparsely granular or fibrillar substance and the re of the cytoplasm is then confined to narrow spaces containing dense packed ribosomes and mitochondria. In the apical part a Golgi apparatu and multivesicular bodies are found, and towards the surface dense ovo granules which may usually measure 0.3 μ and irregular vesicles appe



Fig. 31. The granulated nerve ending (NE_g) innervating a hair cell (*HC*) contains an abundance of synaptic vesicles. An accessory double membrane (*AM*) is seen at the hair cell side of the synapse. *SC* Supporting cell. NE_n non-granulated nerve ending. *SB* synaptic bar. × 33 000

(Fig. 33). A pair of centrioles are present beneath the surface from which 0.1–0.2 μ high microvilli protrude. These microvilli as well as the rest of the cell surface are lined with small granules measuring 100–200 Å (Fig. 33).

The mantle cells surrounding the sensory epithelium are slender cells with basal nuclei. A well developed endoplasmatic reticulum is present throughout the cell though the cisternae are not as distended as is the case in the supporting cells of the hair cell area. Apically a Golgi apparatus, vesicles and secretory granules are seen and the surface membrane forms a few microvilli. Slender mitochondria, dense inclusion bodies, multivesicular bodies and thin bundles of supporting fibrils are also present.

Below the sensory epithelium branching blood capillaries form a dense network (Fig. [illegible]). Towards the basal membrane the capillary wall is very



Fig. 32. At the synapse between a granulated nerve ending (NEg) and a hair cell (HC) the presynaptic membrane (PrM) is separated from the postsynaptic membrane (PoM) by a synaptic cleft which is slightly widened (1) in the vicinity of a synaptic vesicle (SV) and markedly so where one (2) or many (3) ovoid bodies are present inside the synaptic cleft. At these points the accessory double membrane (AM) is affected. Different types of vesicles are seen in the hair cell cytoplasm. R Ribosomes. ×110 000

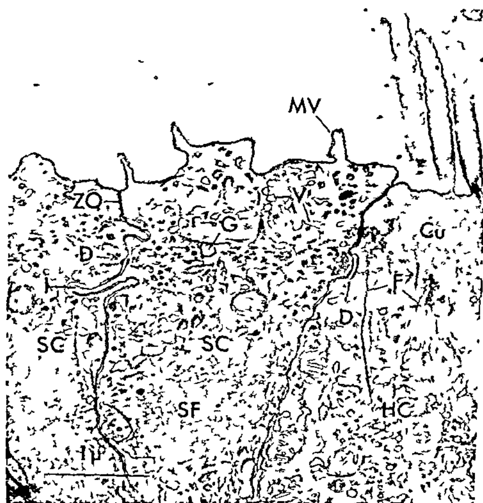


Fig. 33. At the apical interfaces between neighbouring supporting cells (*SC*) a zona occludens (*ZO*), a desmosome (*D*) and interdigitation (*I*) is recognized. Below the surface from which microvilli (*MV*) protrude dense granules (*G*) and vesicles (*V*) are seen. Within the adjacent hair cell (*HC*) filaments (*F*) run from the cuticular region (*Cu*) and downwards. *SF* Supporting fibrils. × 2 000.

thin and is frequently interrupted by about 800 Å wide pores closed by a triple layered membrane (Fig. 35). These pores generally appear two or three together.

Cupula

The bundles of sensory hairs protruding from the sensory cells are lodged in the gelatinous cupula. In sections perpendicular to the sensory epithelium it is seen that the cupula exhibits a longitudinal striation where each dense line emanates from the region of contact between neighbouring



Fig. 34. Section cut parallel to and somewhat below the surface of neighbouring supporting cells which are joined by desmosomes (*D*) from which bundles of supporting fibrils (*SF*) emanate. × 70 000.

cells, as well as a cross striation parallel to the surface of the epithelium. This cross striation is more distinct towards the top of the cupula. It is seen in sections parallel to the sensory epithelium that the cupular material is arranged in a honeycomb pattern (Fig. 36). The cupular substance is made up by a network of fibrils measuring about 100 Å, which are condensed above the cell borders and conspicuously so also above the sensory hair bundle except for a clear canal corresponding to the location of the kinocilium in the sensory hair bundle. Throughout the cupular matrix aggregates of dense granules measuring 100–200 Å in diameter are present. Observations on the fresh cupula reveals its gelatinous structure and manipulation shows that along its margins the cupular substance is stiffer and more resistant to mechanical forces than its central part. This stiff circumferential wall corresponds to the mantle cell zone.

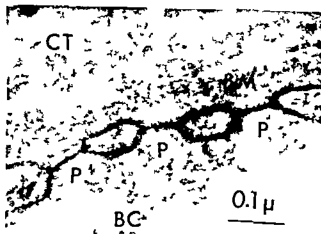


FIG 3a Towards the sensory epithelium the thin endothelial wall of a blood capillary (BC) is interrupted by pores (P) The capillary wall is separated from the connective tissue (*CT*) by a basement membrane (*BM*) × 142 000

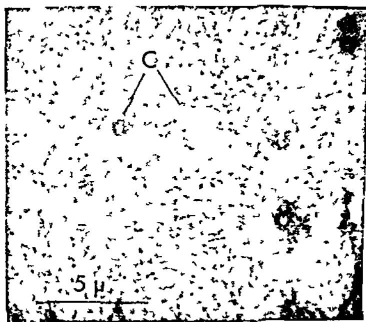


FIG 3c In a rather thick section cut through the cupula parallel to and above the sensory epithelium it is seen that the cupular matrix is condensed (*C*) above the cell borders and conspicuously so above the hair cells At a position corresponding to the location of the kinocilium a clear canal is seen × 5 900

DISCUSSION

Since its discovery in *Lota vulgaris* by Steno (1664) the lateral line system was generally considered as mucus secreting, until 1850 when Leydig presented histological evidence which established its sensory nature Schulze (1861, 1870) described within the sensory organ the termination of nerve fibres on sensory cells provided with apical sensory hairs in the canal organ as well as in the epidermal organ Since then the histology of the lateral line organ has been investigated with conventional light microscopy by several authors (Johnsson, 1917, Woellwarth, 1934, Denny, 1937, Lekander, 1949, Wright, 1951, Dijkgraaf, 1952) but not until recently has the electron microscope been used in the study of this organ The ultrastructure of the epidermal lateral line organ was examined by Trujillo-Cenoz (1961) and unpublished work of Kalmijn on the same organ of frog has been cited by Dijkgraaf (1963) and Görner (1963). Concerning the lateral line canal organ details of synaptic differentiation were reported by Flock and Wersäll (1962 *a*), and Hama (1962) observed the presence of two types of nerve endings in the Japanese sea eel In a paper dealing with the morphological basis of directional sensitivity of the sensory cells, Flock and Wersäll (1962 *b*) described the organization of the sensory hair bundle and the orientation of the sensory cells, and a review of the functional anatomy of the vestibular and lateral line organs (Wersäll and Flock, 1965) provides further information of the fine structure of the canal organ In a recent report Pomes (1964 *a*, 1964 *b*) gives a description of the ultrastructure of the sensory epithelium

The present investigation has been less extensively reported elsewhere (Flock, 1965)

The lateral line canal organ is sensitive to shearing displacement of the cupula in relation to the sensory epithelium caused by movement of the fluid within the canal Because of the location of the canal just beneath the skin the lateral line organs are exposed to mechanical influence from the external milieu and have been shown to respond to the near field displacement caused by vibrating sources in water (Harris and Bergeijk, 1962) and to water displacement caused by moving objects or water currents (Dijkgraaf, 1934) It seems unavoidable that the organ will also be affected by movement of the body of the fish The biological significance ascribed to the lateral line system has been that of a "Ferntastsinn" for detection of moving objects (Dijkgraaf, 1952)

The sensory cells

The sensory cells are flask shaped cells provided with apical sensory hairs and innervated at their bottoms by a number of small nerve endings They resemble the hair cells of the epidermal organ (Trujillo-Cenóz, 1961) as well as of the canal organ of other fishes (Pomes, 1964 *a*, 1964 *b*) and

they are, as it appears, identical in structure with the hair cells of the inner ear sensory epithelia of this fish (Flock, 1964). While they resemble also the hair cells of the labyrinth of other fishes (Wersäll, 1961, Lowenstein *et al.* 1964) of bird (Wersäll, 1961), and of the fowl embryo otocyst (Friedmann, 1959), a more highly differentiated type of hair cells can be distinguished in the vestibular labyrinth of mammals, where the amphora shaped Type I cells (Wersall, 1956) enclosed by a large nerve chalice, are found in addition to the more primitive Type II cells, which correspond to those present in birds and fishes. The presence in the lateral line organ, which belongs to a phylogenetically old system (Pumphrey, 1950) of only one type of cells, which correspond to the Type II cells of mammals, supports the view that in mammals these cells are more primitive than the highly differentiated Type I cell.

The rich contents of small vesicles within the cytoplasm of labyrinthine and lateral line organ hair cells are conspicuous, but the functional significance of these vesicles cannot yet be accounted for. The presence of tubular filaments running from the cuticle downwards within the apical cyptoplasm also attracts attention, but their importance is equally obscure. Similar tubules have been described in the canal organ of another teleost fish by Pomes (1964 *a*) where they were claimed to form the cuticular substance by interweaving of their apical ends. Such an arrangement is not true for *Lota vulgaris* where the cuticular substance is distinct from the tubules.

The sensory cells are provided with sensory hairs, first recognized as such by Schulze (1861, 1870). Due to fixation artefacts and to the limited resolution power of the light microscope, only one conical sensory hair was generally recognized at the top of each hair cell. The splitting up of the sensory hair into a bundle of smaller hairs, recognized as the sensory hairs proper, has been revealed in the electron microscope both in the epidermal organ (Trujillo-Cenoz, 1959) and in the canal organ (Flock and Wersall, 1962 *b*).

Functional significance of morphological hair cell polarization

The sensory hair bundle is composed by several stereocilia and one kinocilium located in the periphery of the bundle as is the case in all organs belonging to the acustico lateralis system except for the cochlea of mammals (Held, 1926, Kolmer, 1927, Wersall, 1956, Engström and Wersäll 1958). The hair cells of the lateral line organ are morphologically polarized not only by the presence of a kinocilium in the periphery of the sensory hair bundle, but also by the stepwise increasing length of the stereocilia which become taller towards the kinocilium (Flock and Wersall, 1962 *b*) as is the case also in the inner ear of mammals (Engstrom *et al.* 1962).

It was found by Flock and Wersall (1962 *b*) that in the lateral line canal organ this morphological polarization coincides with a directional sensitivity of the individual hair cell in such a way that displacement of the cupula

in a direction away from the stereocilia towards the kinocilium is exci-
tory, leading to a depolarization and an increased discharge rate in the inn-
vating nerve fibre whereas cupular displacement in the opposite direct
is inhibitory, leading to hyperpolarization and decrease of discharge r
This conclusion was based upon a similar correlation of morpholog
and functional polarization observed by Lowenstein and Wersall (1959)
the crista ampullaris of the ray, and derived from the presence in t
lateral line canal organ of two about equally large groups of hair ce
oriented with their kinocilia pointing in opposite directions along the ca
(Flock and Wersall 1962 *b*) This theory accounts for the presence in t
nerve innervating each organ of two groups of nerve fibres which fun
tionally oppose each other in terms of directional sensitivity (Sand 193
and it explains the double frequency of the microphonic effect, in relati
to the frequency of the stimulus, by the superposition of antagonistic
sponses derived from the two groups of cells It is then a prerequisite co
dition that the depolarization caused by one group of cells is larger than t
hyperpolarization simultaneously evoked by the oppositely oriented gro
of cells otherwise the opposing potentials would cancel each other Simil
conclusions were arrived at by Dijkgraaf (1963) and by Gorner (1963) f
the epidermal organ of the frog from a correlation of the electron micr
graphs of Kalmijn to the electrophysiological studies of Gorner (1961 196
A recent electrophysiological investigation which is described below, h
verified the validity of this theory and also shown that displacement of t
sensory hairs in a direction perpendicular to the orientation of the cell
ineffective as a stimulus as would be expected from the theory

In macula utriculi of *Lota vulgaris* the orientation of the sensory cells
related in the same way to the electrophysiological properties of the org
(Flock 1964) It is consequently possible to examine *in vitro* the pattern
directional sensitivity of a whole organ on a cellular level by mapping wi
the electron or phase contrast microscope the orientation of the senso
cells as revealed by the position of the kinocilium Such mapping has r
cently been carried out on the entire labyrinth of the ray by Lowenste
et al (1964) on the macula utriculi of the monkey by Spoendlin (196
and on the same organ of the fish by Flock (1964)

The directional sensitivity of the hair cell is indicated not only by th
position of the kinocilium in relation to the stereocilia but also on an ultr
structural level by the asymmetric arrangement of the component filamen
of the kinocilium and by the presence of a basal foot which protrudes fro
the basal body away from the stereocilia that is in the direction of excit
tory stimulation The presence of a *basal foot with a similar relation t*
the functional polarization of the cell has been observed in the ray labyrint
(Lowenstein *et al* 1964) and in the macula utriculi of *Lota vulgari*
(Flock 1964) The ultrastructure of this region has been reconstructed fro
high resolution pictures of serial sections (Flock and Duvall 1965) It i
interesting to observe in motile cilia the correlation of an analogous mor

phological polarization of the kinocilium and its basal body to the beating direction of the cilia (Gibbons, 1961, Afzelius, 1961), a fact which directs our attention to the presence of modified cilia also in other sense organs It has been suggested by Lowenstein *et al* (1964) that the kinocilium may act as a motile cilium in the reverse by responding to passive deformation in a certain direction with the initiation of electric change as proposed for the tympanic organ by Gray and Pumphery (1958) It must be recalled, however, that the hair cells in the organ of Corti exhibit distinct directional sensitivity (Bekesy, 1953) in spite of the fact that they lack the kinocilium (Engström and Wersall, 1958) They do possess a centriole, which is considered the equivalent of the basal body of the kinocilium, and which, in the outer hair cells, indicates by its position the directional sensitivity of the cell (Flock and Wersäll, 1963, Engström *et al* 1962, Flock *et al*, 1962), a fact which has been interpreted by Engström *et al* (1962) as implying that in the organ of Corti it is the centriole which is the essential excitable structure It is, however, generally believed that the stereocilia are engaged in the initial stages of sensory perception in the hair cells, that is the transduction of the mechanical energy of cupular displacement to the bioelectric receptor mechanism, and should therefore be considered as the primarily excitable structures The role of the kinocilium is still obscure While it is conspicuous that the directional sensitivity of the vestibular and lateral line hair cells is indicated by the position of the kinocilium and by its asymmetric structure, it must be recalled that this correlation can be applied also to the stepwise increasing length of the stereocilia, to the arrangement of the stereocilia and their rootlets, and to the structure of the cuticular plate, all these being consistently present features of polarization which are also exhibited by the hair cells of the organ of Corti where the kinocilium is lacking At the present time it is difficult to judge upon which structure the directional sensitivity of the hair cell is dependent

Innervating nerve fibres

The nerve trunk innervating each organ comprises myelinated and unmyelinated nerve fibres which exhibit the fine structure common to peripheral nerves (Robertsson, 1955, Elfvin, 1961) The myelinated nerve fibres range from 1 to 25 μ in diameter and they are distributed in two distinct groups having the mean diameters of 4 μ and 12 μ respectively

The range of fibre calibres approximately corresponds to that encountered in other lateral line organs both of the canal type (Katsuki *et al* 1951 *a*) and of the epidermal type (Murray, 1955) whereas the nerve fibres reaching the mammalian labyrinthine organs are smaller ranging from about 1–10 μ (Engström and Rexhed, 1940, Wersäll, 1956 Rasmussen, 1940) In these other cases the frequency distribution curves show, however, only one peak

Unmyelinated fibres have earlier been observed in the canal organ of eel

by Hama (1962) and in the mammalian vestibular nerve by Wersall (1960)

Within peripheral nerves it has long been attempted to ascribe different functions to nerve fibres of different diameters It is known that the labyrinthine organs are innervated by efferent as well as by afferent nerve fibres (Petroff 1955, Rasmussen, 1960 Gacek 1960) and efferent nervous activity has also been recorded at these organs (Fex 1962 Gleisner and Henriksson 1964 Schmidt, 1963) It also seems that the epidermal lateral line organ of amphibians receives an efferent input (Schmidt 1964) In this organ afferent impulses have been recorded from the thick fibres 8–18 μ in diameter by Gorner (1963) who suggests an efferent function to the thin fibres, 3–5 μ in diameter, which are also present It is interesting to note that the efferent fibres innervating the mammalian labyrinthine organs have a diameter of 3–5 μ in the cochlear nerve (Rasmussen 1960) and 2–5 μ in the vestibular nerve (Gacek 1960)

Many mechanoreceptors are phasic tonic meaning that two classes of sensory units can be distinguished according to their different threshold and adaptation times The slowly adapting low threshold tonic units signal at a maintained firing rate the extent of stimulation while the phasic units adapt quickly and have a relatively high threshold Phasic units which tend to be served by thicker and more rapidly conducting fibres are believed to represent a phylogenetically recent system and subserve sensory discrimination (Davis, 1961 Kennedy 1962) Such different functions have been ascribed to the thin and thick fibres respectively in the lateral line canal organ by Katsuki et al (1951 c) These authors reported the termination of thick fibres in the centre of the epithelium while thinner fibres ended in the periphery There is no such specific distribution in the canal organ of *Lota vulgaris* but a similar distribution was found by Wersall (1956) in the crista ampullaris of the guinea pig where thick fibres innervate centrally located Type I cells while peripherally located Type II cells are innervated by thin fibres which end throughout the sensory epithelium In the lateral line organ no distinction can however be made between Type I or Type II cells

The possibility also exists that the two groups of fibres may innervate respectively the groups of hair cells which are oriented in opposite directions

The unmyelinated fibres are similar in structure to those described in vestibular nerve branches by Wersall (1956) It has not been possible to identify their destination and neither is it known if they represent afferent or efferent pathways Unmyelinated nerve fibres are seen to penetrate through the basement membrane and travel among the sensory supporting cells but it has not been established if they derive from the unmyelinated f[illegible]s in the innervating nerve as claimed for the canal organ of shark [illegible]sson 1917)

[illegible] ssibility that unmyelinated fibres reaching the cristae ampullares in [illegible] ea pig might have a vegetative origin and serve a vasomotor

function or innervate directly the sensory cells has been discussed by Wersäll (1960) Indirect influence of the vegetative system on the response of sensory organs through vasomator control has been claimed for the olfactory mucosa (Beidler, 1960), but such influence is not accepted as a common phenomenon, neither has the response of a sensory organ been shown to be influenced by the direct action of autonomic fibres (Davis, 1961) It has to be pointed out, however, that granulated vesicles similar to those observed in many unmyelinated fibres in the present investigation have been suggested as a site of binding of catecholamines particularly noradrenaline, within the nervous system and in neurosecretory organs, including axons of peripheral autonomic fibres (De Robertis, 1964) Granulated vesicles are present in many of those nerve endings which are considered efferent but are seen equally often in the afferent endings, and it is not justified to identify these nerve endings as the terminations of the unmyelinated nerve fibres by the presence of such vesicles It may equally well prove that the unmyelinated fibres are afferent or efferent somatic fibres which innervate the hair cells and convey impulses of sensory nature

As yet there is no experimental evidence which conclusively ascertains specific functions to the different groups of nerve fibres and whereas such correlation may exist in certain respects within the nervous system (Gasser, 1955), it is now currently realized that overlapping may exist (Bishop, 1959)

In each organ several hair cells are innervated by the same nerve fibre as is the case also in the utricular macula of *Lota vulgaris* where the convergence approximates 10 to 1 (Flock 1964) Such an arrangement may serve to lower the threshold of a nerve fibre by spacial summation of subliminal stimuli (Davis, 1961)

Nerve endings

The innervation of the lateral line hair cells has been intensively studied by conventional histological methods but conflicting results have been gained by different authors and for different organs and animals Nerve fibres have been described to end with terminal knobs (Johnsson, 1917, Heilig, 1912) or to terminate as a basket like network at the base of the cell (Bunker, 1897) Charriper (1928) and Chezar (1930) claimed to have seen intracellular nerve endings In an electron microscopic investigation Trujillo Cenoz (1961) distinguished in the epidermal organ between nerve endings deeply recessed in the cytoplasm, calyx type and knoblike endings In the canal organ of *Lota vulgaris* nerve endings of different size and appearance establish synaptic contacts of various types as described above, and it is possible to reveal their exact topographical distribution only by three dimensional reconstruction from serial sections It is evident, however, that nerve endings of the calyx type innervating the Type I hair cells in mammalian vestibular organs (Wersäll 1956) are not present in the lateral line canal organ

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The possibility that unmyelinated fibres reaching the cristae ampullares in the guinea pig might have a vegetative origin and serve a vasomotor

The elaborate ultrastructure of the synaptic region at the synaptic bar vastly resembles that of the Type 1 axodendritic synapse in the central nervous system (Whittaker and Gray 1962), a cluster of vesicles surround the synaptic bar at the hair cell side of the synapse, the nerve ending plasma membrane is more heavily outlined than that of the hair cell and along it runs a thin membrane in the synaptic cleft Accordingly, the plasma membrane of the hair cell corresponds to the presynaptic and that of the nerve ending to postsynaptic membrane and the direction of transmission is from the hair cell to the nerve ending It is believed that the active point of the synapse is at the synaptic bar and that this is where the afferent impulse is initiated The synaptic bar seems to be a distinguishing feature of afferent synapses in sensory organs although synaptic bars are present also at other sites within the nervous system (Castejon and Villegas 1964) Its presence in organs responding to so different kinds of stimulation has been interpreted as implying a common process of synaptic transmission in these organs (Barets and Szabo, 1962) It is not known if the afferent nerve endings in the labyrinthine and lateral line organs are electrotonically excited or if spike initiation depends on neurohumoral transmission but the latter view is generally favoured (Davis 1961) It lies close at hand to suggest the vesicles surrounding the synaptic bar as representing a site of binding of transmitter substance analogous to the synaptic vesicles in the presynaptic cytoplasm of other synapses

Supporting cells

The structure of the sensory supporting cells is suggestive of their sustentacular function as well as of secretory activity Along their apical circumference and also further down they are joined to each other and to the hair cells by desmosomes from which bundles of supporting fibrils emanate and below the surface extensive interdigitation is seen This way the hair cells are rigidly interlocked in the sensory epithelium The size and appearance of the endoplasmatic reticulum implies a great secretory capacity as is the case also in other fishes (Hama, 1962 Pomes 1964 *a*) The bulk of the cupula is greater than that of the thin otolithic membrane in the macula utriculi of this fish where the endoplasmatic reticulum is also less extensive It is not known whether the secretory activity of the supporting cells is only devoted to the formation of the cupular substance, or if it also contributes to the canal lymph While the source of the canal lymph is unknown, it is realized on account of its ionic contents (Wersäll and Flock 1964), that it is distinct from the sea water with which the canal communicates The mantle cells, which surround the sensory supporting cells have an appearance and extend up the walls of the canal in a fashion reminding of the planum semilunatum of the guinea pig crista ampullaris to which secretion of endolymph has been attributed (cf Kimura Lundquist and Wersäll 1964) The zone of mantle cells is however, covered by the

peripheral parts of the cupula, and must therefore contribute also to the formation of the cupular matrix

The wall of the capillary network which supplies the entire epithelium displays frequent fenestrated pores similar to those significantly found in places where passage of fluids takes place (cf. Rhodin, 1962). Such pores have recently been found also in the endolymphatic sac of the guinea pig labyrinth (Lundquist *et al*, 1964; Lundquist, 1965).

Cupula

The cupula of the lateral line organ was first observed by Schulze (1861) and it has been described as a honeycomb framework derived from the borders of the supporting cells (Denny, 1937) analogous to the cupula of the crista ampullaris (van der Stricht, 1921). It is confirmed in the electron microscope that the cupular fibrillar matrix is condensed along the borders of the supporting cells It is also observed that a dense cupular matrix which extends above each sensory cell establishes contact with the sensory hair bundle through the fibrillar meshwork which is interwoven between the stereocilia This coupling is believed to serve the transmission of cupular displacement to the sensory cells

It is believed that the cupular substance is secreted from the apical surface of the supporting cells The condensation of fibrillar material above cell borders and hair cells might be accounted for by the higher rate of continuous secretion at the active surface of the supporting cells than at their interfaces The somewhat stiffer character of the walls of the cupula might be accounted for by the fact that this part of the cupula derives from the mantle cell zone and not from the sensory supporting cells

SUMMARY

The general structure of the lateral line canal organ and the fine structure and innervation of the sensory epithelium was studied by dissection, and by light and electron microscopy

Each sensory organ is situated at the bottom of the canal which is supported at each organ by an osseous half cylinder The sensory epithelium rests upon a stiff oval disc formed by the branching nerve fibres innervating the sensory cells It is bordered by a zone of mantle cells which extend somewhat up the walls of the canal The flask-shaped hair cells are surrounded by supporting cells, and are provided with a bundle of apical sensory hairs, which project into the overlying gelatinous cupula

The ultrastructure of the receptor cells resembles that of labyrinthine hair cells of fish and of the Type II cells of the mammalian inner ear

The fine structure and organization of the sensory hair bundle are described Each sensory cell is morphologically polarized by the presence of a kinocilium in the periphery of the bundle, and adjacent hair cells are

oriented with their kinocilia pointing in opposite directions, towards the head and towards the tail alternatively, but always along the axis of the canal These findings are discussed in terms of directional sensitivity

The innervating nerve contains myelinated and unmyelinated nerve fibres Two groups of myelinated nerve fibres can be distinguished, having the average diameters of 4 μ and 12 μ as revealed by calibre analysis The possible roles of the different types of nerve fibres are discussed

The hair cells are innervated by two types of nerve endings, non-granulated and granulated ones The non-granulated nerve endings, which are regarded as the afferent sensory terminals, are characterized by the presence of a synaptic bar at the hair cell side of the synapse The granulated nerve endings are believed to represent the terminations of the efferent nerve fibres, and are characterized by their content of synaptic vesicles and by the presence, inside the hair cell, of an accessory double membrane apposed to the synaptic region As regards the appearance of the afferent and efferent synapses, the resemblance of the hair cells with neurons of the central nervous system is evident, the afferent synapse corresponds to the axodendritic type and the efferent synapse to the axosomatic type

The morphology of the supporting cells is suggestive of their sustentacular function as well as of secretory activity The structure of the cupula is described and its formation and the origin of the canal lymph in discussed

The Microphonic Potential of the Lateral Line Canal Organ

INTRODUCTION

On the basis of expanded knowledge of sensory physiology arrived at in recent years it has been attempted to generalize the principles of sensory perception in the various sensory organs into a universally applicable general theory of receptor action (Gray, 1959; Davis 1961). It is evident that the success of such an enterprise depends on the identification of the basic sensory mechanism common within each group of related organs. The acustico-lateralis organs have the same embryological origin and also display a similar basic structure. The mechanical coupling of the sensory units to auxiliary structures of different types, in each case determines the specificity of an organ to a particular type of stimulus (Pumphrey, 1950, Lowenstein, 1956). The biological significance of the various organs may therefore differ, while the adequate stimulus for the sensory cells and their mode of action is still the same. When such considerations are taken into account certain differences still seem to exist between the electrophysiological properties of the various organs belonging to the acustico-lateralis system. Such a difference concerns the fact that the frequency of the microphonic potential in the lateral line canal organ is twice that of the stimulus (Jielof *et al.*, 1952), while in the cochlea (Tasaki *et al.*, 1954) and in the cristae ampullares of the semicircular canals (de Vries and Bleeker, 1949) it follows the frequency of the stimulus. This inconsistency implies discrepant receptor mechanisms in closely related organs and its illusory nature can only be concealed on a cellular level. Since intracellular recordings of receptor potentials have not yet been obtainable within the acustico-lateralis system, the gain of information still depends on indirect methods. A theory for the function of the hair cells of the lateral line canal organ, which accounts for the double frequency of the microphonic potential on the basis of the directional sensitivity of the individual sensory cell, has been arrived at from a correlation of functional and morphological polarization (Flock and Wersäll, 1962 *b*). The theory also applies to the labyrinthine organs where a similar correlation exists (Lowenstein and Wersäll, 1959).

The aim of the present investigation was to study the quantitative stimulus-response relationship between the microphonic potential generated by the sensory cells and a well calibrated stimulus of adjustable amplitude and direction. For this purpose a method had to be adopted by which the stimulus is transmitted to the sensory cells with as little intervention as possible of the mechanical properties of the cupula and the canal lymph.

In earlier electrophysiological studies on the lateral line canal organ the stimulating techniques used have comprised indirect stimulation by distant vibrating sources, or by steady or alternating water currents directed towards the canal (Katsuki *et al* 1951 *b*, Suckling and Suckling, 1950, Harris and Bergeijk, 1962) or affecting directly the organ (Sand, 1937, Jielof *et al* 1952), or with a magnet attached to the cupula (Kuiper, 1956) By none of these methods the amplitude and the direction of cupular displacement can be quantitatively controlled with a satisfactory degree of accuracy The nature of the attempted investigation therefore prompted the development of a stimulating technique which allowed direct static transient or vibratory stimulation of controllable amplitude and direction

MATERIALS AND METHODS

Preparation

The organ studied was the third left supra temporal lateral line canal organ of the isolated head of the teleost fish (burbot) *Lota vulgaris* The anatomy and ultrastructure of this organ has been described in the preceding section

Thirty-eight animals were used for the present study The animal was immobilized by transection of the spinal cord at the cervical level and the skin was cut away above those parts of the supra temporal and infra-orbital canals which constitute the extension of the mid body canal The infra orbital portion of the exposed canal was closed with a piece of cotton soaked in paraffin oil, and in a similar manner the canal was closed at the level of the fourth supra temporal organ The animal was then decapitated and the isolated head was mounted in a head holder attached by a ball and socket joint to a brass basement or alternatively to a rotating table, mounted with manipulator grease on the stand of a Zeiss micromanipulator (Fig 37) Final dissection was continued under a Zeiss preparation microscope and was performed with the aid of watch maker's forceps and small knives made from the edges of razor blades The organ was exposed by gentle removal of the membranous canal roof covering the sensory area (Fig 38) Even though dissection was carried out most carefully the cupula is easily damaged during the preparation Such damage is probably caused by excessive and uncontrolled movement of the canal lymph

The exposed organ is located at the bottom of the isolated portion of the canal which is filled with viscous canal lymph The gelatinous cupula has the same refractive index as the canal lymph and in order to enable a proper fitting of the stimulating tube around the top of the cupula, the outlines of the cupula have to be made visible This was achieved by directing a fine jet of zinc oxide suspension towards it with the aid of a micro-capillary pipette (Jielof *et al* 1952) Particles of zinc oxide then

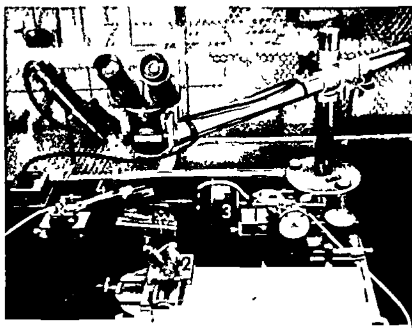


Fig. 37. Photograph showing the experimental set up. The isolated head is mounted in a head holder (1) attached to a rotating table (2). The vibrator (3) by which the organ is stimulated is attached to a micromanipulator provided with indicator clocks which read the position of the stimulating tube. The microphonic potential is picked up with an electrode mounted in the left hand manipulator (4).

adhere to the surface of the cupula. No difference could be observed in the microphonic output of organs to which zinc-oxide had been applied and such where the cupula had been made visible by temporary withdrawal of the canal lymph when the stimulating tube was fitted. Staining with cold Indian ink or with methylene blue proved less appropriate since in these cases the cupula was less distinctly outlined.

Additional experiments were performed in intact fishes in order to establish that the decapitation did not influence the functional properties of the organ. Fishes were then immobilized with curare, the head fixed with a biting piece and the body rested in a shallow tray. Artificial respiration was maintained by leading tap-water through the mouth and out of the gills. After the experiment it was established that the fish was still alive by watching the flow of red blood corpuscles in the capillaries leading to the organ. In no respect did the results obtained from the isolated organ noticeably differ from the recordings on the intact fish. In the course of time the microphonic output of the isolated preparation decreases, but reliable experimentation could be made for four or five hours. In several cases a microphonic output could still be recorded seven hours after decapitation. Influence of efferent activity may well exist in the living fish

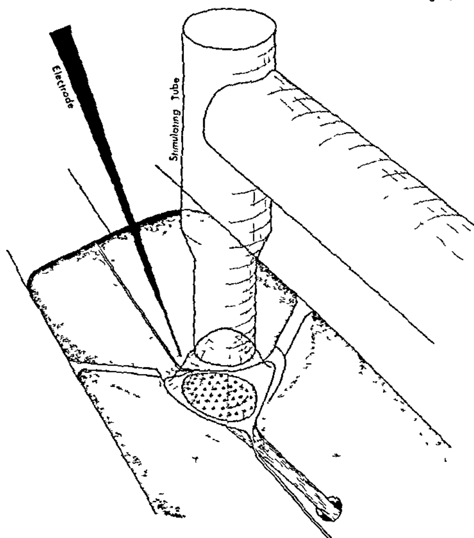


FIG 38 Schematic drawing showing the application of the stimulating tube to the cupula and the position of the recording electrode in relation to the sensory epithelium

under certain conditions Whether efferent neurons are active in the isolated preparation was not controlled

Properties of Stimulating Device

The organ was stimulated with a vibrating glass tube fitted around the cupula The arrangements for generation of mechanical stimulation of the cupula is shown schematically in Fig 39 The stimulating tube was attached to a vibrator (Goodman, Model V 47) driven from a sine-wave generator (GR Type 1302-A) via a power amplifier (Quad II) and a variable attenuator In addition facilities for superimposing a direct current to the

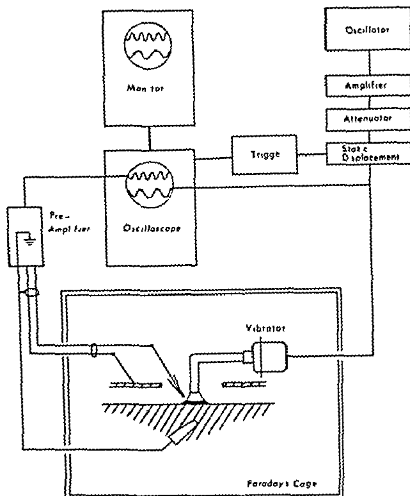


Fig. 39 Block diagram showing the arrangement of the stimulating and recording device

vibrator for the purpose of producing a suddenly applied transient or static displacements was incorporated. The frequency range used was 10–1,000 cps. The vibration amplitude could be adjusted with the variable attenuator.

In the actual experiment the vibration amplitude was not determined but the stimulation was monitored by the electrical signal applied to the vibrator. *The relationship between the vibration amplitude and the electrical* signal applied to the vibrator was determined by means of a capacitive probe which did not load the vibrating system (Møller, 1963). The relation between the electrical signal and the vibration was determined with respect to amplitude as well as to phase angle. At any fixed frequency the vibration amplitude is a linear function of the driving voltage. The absolute half peak to peak amplitude of the vibrating tube was measured in a microscope provided with a measuring eye piece. From such measurements the relation between the vibration amplitude in microns and the driving voltage

was determined. At 100 cps 0.19 μ per 1 mV was yielded. Consequently in the course of the experiment the driving voltage could be used as a measure of the vibration amplitude. The relation between the electrical current applied to the vibrator and the vibration amplitude is, however, frequency dependent. The phase angle between the electrical signal driving the vibrator and the vibration amplitude as a function of frequency is seen in Fig. 43. The resonance frequency was about 105 cps. The impulse response of the vibrator was also determined by recording the vibration amplitude produced by a short rectangular impulse applied to the vibrator (Fig. 44 a). From these results the damping of the transducer was estimated to be somewhat less than critical.

Apart from the vibratory stimulation provided by the vibrator the cupula could be given a constant static displacement with the aid of the manipulator. The magnitude of displacement could be read in units of 1 μ on an indicator clock which measured the motion between the sliding surface of the manipulator. Sideways displacement was controlled in a similar manner. The manipulator does not allow quick horizontal movement. Transient displacement or lasting displacement with a steep rise time was therefore produced by a variable DC current through the vibrator coil. The direction and the amplitude of displacement was controlled by changing the direction and the strength of the current. The DC current could be switched on by hand or with a relay driven with a Grass stimulator. The frequency, the duration and the delay of the displacement could be regulated with the stimulator, which was also used to trigger the sweep of the oscilloscope.

The input to the vibrator was recorded on the lower beam of a double beam cathode ray oscilloscope (Type 502 Tectronix).

Application of Stimulus to the Organ

The organ was stimulated with a vibrating glass tube fitted around the top of the cupula (Fig. 38). In each case the tube used had a diameter to match that of the cupula and ranged from 0.5–0.8 mm. The diameter of the organ is generally about 1 mm. The stimulating tube was attached at right angles to the vibrator which was mounted horizontally on the right hand Zeiss micromanipulator (Fig. 37). The organ was oriented horizontally with the axis of the canal parallel to the movement of the vibrator rod except in the experiments on directional sensitivity where different stimulating directions could be selected. In the standard experimental condition the head was oriented with the snout pointing towards left. Canal lymph was allowed to suck up by capillary force into the tube before it was lowered around the cupula with the aid of the micrometer drive of the manipulator. The level of canal lymph was normally kept at the lower margin of the stimulating tube thus covering the exposed part of the cupula. Consequently the organ as well as the top of the cupula were surrounded by physiological canal fluid much as in the natural situation. The m

scope lamp was equipped with an infrared filter in order to reduce evaporation, and in the course of the experiment the level of the fluid could be kept constant by adding canal lymph sampled from the right side of the head or from other fishes

The fitting of the stimulating tube around the cupula was controlled in the dissecting microscope, but to ensure an optimal coupling, final vertical adjustment had to be checked by electrophysiological measurements, as will be described below The vertical position of the tube could be read in units of 10 μ from an indicator clock, which was attached to the manipulator

Recording

The microphonic potential was recorded in the canal lymph at the rostal margin of the organ with a chlorated silver electrode, 50 μ or 100 μ in diameter, isolated with lacquer except for the tip (Fig 38) This type of electrode gives a correct reproduction of AC voltages, and allows sufficiently stable DC recording for the measurements made The electrode was attached to the left hand micromanipulator (Fig 37) In the case of recording with differential leads, the indifferent electrode, which was also a chlorated silver wire, was pushed into the connective tissue outside the canal and about 1–2 cm away from the organ For AC recordings the electrodes were connected to a Type 122 Tectronix preamplifier and the preparation was grounded to the input of the preamplifier with a chlorated silver plate pushed into the tissue at the side of the head In the case of DC recordings a cathode follower and a Grass P6 preamplifier were used In the experiments on the directional sensivity of the organ, the active electrode was introduced from above into the stimulating tube and the microphonic potential recorded in the canal lymph sucked into the tube The indifferent electrode was then grounded at the input of the preamplifier The microphonic output was visualized on the upper beam of the oscilloscope from which photographs could be taken with a polaroid camera (Hewlett Packard) When the camera was attached to the oscilloscope a second oscilloscope was used as a monitor (Type 502 Tectronix)

The whole experimental set-up was located inside an electrically floating Faradays cage, measuring 2 5 × 1 5 × 2 m, made by a double layer of chicken net, which provided satisfactory shielding from external electrical fields With an open input the noise level was about 10 μV peak to peak and with the electrodes in recording position it was considerably less and allowed the identification but not the quantitative analysis, of signals in the order of 1 μV For measurements at a high sensitivity the most disturbing "noise" was caused by mechanical vibrations transmitted from the building to the preparation and to the stimulating tube In order to diminish such disturbances the micromanipulator stood on hard rubber sockets on a 200 kg iron platform resting on a concrete basement with rubber cushions between The weight of the basement was about 600 kg and it stood on

a wooden frame on the ground floor With this arrangement spurious low frequency vibrations produced a microphonic potential of 10 μV at the most

EXPERIMENTS

The aim of the investigation was to study

1 the quantitative relation between the amplitude of the stimulus and the microphonic potential output,
2 the magnitude of the microphonic output at different stimulating directions,
3 the effect of static displacement on the microphonic potential and
4 the variation of the DC level during the generation of the microphonic potential

To enable an accurate interpretation of the experimental results a series of basic experiments were performed in order to investigate

(a) the wave shape of the microphonic potential,
(b) the phase characteristics of the microphonic potential
(c) the significance of the application of the stimulus to the organ and
(d) the significance of the recording conditions on the microphonic output

Basic Experiments

The wave shape

This paragraph concerns the analysis of the wave shape of the microphonic potential and the significance of a proper control of the wave shape in the standard experiment

Experimental condition The organ was stimulated along the axis of the canal with a frequency of 100 cps In each experiment with a stimulus of a constant amplitude but at a different degree of static cupular displacement The coupling between the stimulating tube and the cupula was optimal (page 60) and the microphonic potential was recorded with the electrode in the standardized position (page 61 and Fig 38)

Results It is a characteristic feature of the microphonic potential in the lateral line organ that it has a frequency twice that of the stimulus [illegible] (Fig 40 *a*) A transient displacement in either of two opposing directions causes a negative potential (Fig 41) a fact demonstrating that the [illegible] phonic output is composed by negative peaks only one negative [illegible] responding to each swing of the vibrating cupula in either [illegible] microphonic potential normally has a symmetrical and [illegible] shape As will be shown in a following section the wave shape [illegible] phonic potential is gradually changed when cupula is given a [illegible] placement It is transformed into the frequency of the stimulus [illegible] has given exceeds the vibration amplitude The wave shape [illegible] sistently found to diverge from the sinusoidal shape [illegible] positive peak (Fig 40 *b*) In cases of partial static [illegible] of the two

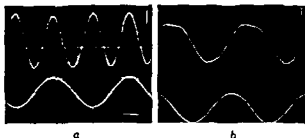


Fig. 40 (*a*) Normal microphonic potential (upper beam) in response to a sinusoidal stimulus (lower beam). (*b*) Appearance of the microphonic potential when the cupula is given a static bias larger than the vibration amplitude. (*a*. Time bar 2 msec, vibration amplitude 4 μ, vertical bar 20 μV. *b*. Time bar 2 msec, vibration amplitude 4 μ, vertical bar 50 μV.)

negative peaks are not equally large in as much as every second peak is smaller than its neighbours. In the standardized experiment this asymmetry has to be controlled by adjusting the position of the vibrating tube in the appropriate *direction along the canal*, since values obtained from an asymmetric output are not correlated in an accurate way to the amplitude of the vibration (page 76). When such compensation is performed in organs where the asymmetry depends on serious damage to the cupula the sine wave shape will be distorted (Fig. 42) and such organs may not be used when critical measurements of input-output relations are to be made.

Conclusion. It is of significant importance that the wave shape of the microphonic potential is controlled at the beginning of each experiment.

Discussion. The microphonic potential in the lateral line organ was discovered by de Vries (1948) and further studied by Jielof *et al.* (1952), Kuiper (1956), Harris and Bergeijk (1962) and others. In this organ the frequency of the microphonics is twice that of the stimulus, while in the cochlea (Tasaki *et al.* 1954) and in the crista ampullaris (de Vries and Bleeker, 1949) it follows that of the stimulus. In the otolith organs microphonic frequencies other than that of the stimulus have also been observed (Zotterman, 1943, de Vries, 1956). With a non-biased cupula the microphonic potential in the lateral line organ has a sinusoid wave shape, while at other instances aberrations from the sine wave shape are seen. Similar

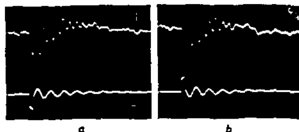


Fig. 41. Microphonic response to stimulation starting with (*a*) rostral and (*b*) caudal cupular displacement. Time bar 10 msec, vertical bar 10 μV.

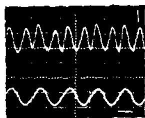


Fig 42 Microphonic potential showing distortion of the wave shape (Time bar 5 msec vibration amplitude 4 μ vertical bar 20 μV)

aberrations are to be seen from the figures of Jielof *et al* (1952) and Kuiper (1956) The significance of the double frequency of the microphonic potential in the lateral line organ will be discussed in a following paragraph (page 70) which deals also with the wave shape of the microphonics

The Phase Characteristics

It is an important question whether the microphonic response follows the amplitude or the velocity of the cupula This question is not only of a theoretical interest, but also concerns the efficiency of the transmission of the stimulus to the sensory cells and therefore the accuracy of the stimulating technique developed

Experimental condition The organ was stimulated along the axis of the canal with constant stimulating amplitude and at optimal coupling between the stimulating tube and the cupula (see following section) The microphonic output was recorded at the rostral margin of the sensory epithelium The stimulus used was a) vibratory stimulation within the frequency range 10–200 cps and b) a transient displacement

The temporal relation between the displacement of the stimulating tube and microphonic potential was measured on the oscilloscope with the driving voltage fed to the vibrator as a reference

The net phase shift produced by the experimental apparatus is the sum of that produced by the stimulating apparatus and the recording apparatus The phase shift produced by the recording amplifier was determined by applying a constant AC current to the recording electrode when it was inserted into the preparation and reading the phase shift between this current and the electrical output from the amplifier It was found that this phase shift increased towards higher frequencies but that it did not exceed 5°–10° at 200 cps

Results a) *Vibratory stimulation* The phase difference between the driving voltage and the amplitude of the vibrating tube was measured at different frequencies with the capacitance probe and plotted in a diagram (Fig 43) The phase relation between the driving voltage and the microphonic effect was determined and plotted in the same diagram It is seen from this figure that the phase of the microphonics follows that of displace

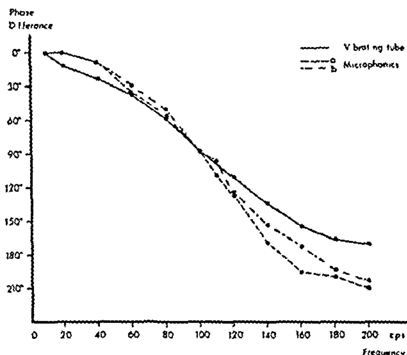


Fig. 43. Diagram showing the phase difference between the voltage driving the vibrator and the vibration amplitude, and between the same voltage and the microphonic potential in two different organs (*a* and *b*).

ment and not velocity in which case it would have been 90° ahead of the displacement of the tube at all frequencies.

b) *Transient Stimulation.* For the transient stimulus the impulse response of the vibrator was determined with the capacitance transducer and appears from Fig. 44 *a*, which shows the amplitude of the vibrator when a transient driving impulse was applied. The microphonic potential generated by the same transient stimulus appears from Fig. 44 *b*. Fig. 44 consequently illustrates the temporal relationship between the displacement of the stimulating tube and the microphonic output generated by this stimulus. It is seen that the microphonic potential follows the displacement of the stimulating tube and not the velocity. The extremes of each wave of the damped oscillations correspond to a negative peak in the microphonic potential. In the case of a transient stimulus the microphonic potential consequently is a measure of displacement and not velocity.

Conclusion. The microphonic potential expresses the amplitude and not the velocity of the stimulus.

Discussion. It is well known that in simple mechanical systems consisting of only one mass-element, one stiffness and one friction-element, the displacement lags 90° behind the driving force at the resonance frequency. The resonance frequency of the vibrator is 100–110 cps, and this is also approximately where the inflection of the phase difference curve occurs.

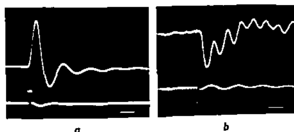


Fig 44 (*a*) The impulse response of the vibrator measured with a capacitance transducer (Time bar 5 msec) (*b*) Microphonic potential generated by the equivalent stimulus (Time bar 5 msec vertical bar 20 μV)

In a vibrating system consisting of two firmly coupled mechanical systems corresponding in our case to the stimulating tube and the cupula they will behave like a single system The resonance frequency is determined by their added mass and elasticity Compared to the mass of the vibrator piston (6 5 g) the mass of the cupula (≈0 5 mg) is negligible and will not noticeably alter the frequency characteristics of the vibrator The same is true for elasticity

It was found that at vibratory as well as transient stimulation the microphonic potential is closely related to the motion of the stimulating tube In both cases it was found that the microphonic potential expresses the amplitude and not the velocity of the stimulus as has earlier been shown by Jielof *et al* (1952) Kuiper (1956) and Harris and Bergeijk (1962) In the cochlea Békésy (1951 *a*) has shown that displacement and not velocity generates the microphonic potential and also in the otolith organs displacement is the effective stimulus (Holst 1950) From the phase measurements it appears that the method of stimulation used provides an efficient direct transmission of the stimulus to the sensory cells At 100 cps the microphonic effect closely follows displacement At lower frequencies it is somewhat ahead and at higher frequencies it lags behind displacement These findings agree with the observations of Kuiper and were explained by him as due to a slip effect of the sensory hairs at low frequencies and a latency of the microphonic response at high frequencies

The Application of the Stimulus

This experiment was performed to investigate the influence of the degree of coupling between the stimulating tube and the cupula as controlled by the vertical position of the tube above the sensory epithelium on the microphonic output

Experimental condition The stimulating tube was vibrating parallel to the axis of the canal with a constant amplitude at a frequency of 100 cps The output was recorded at the standard position (page 61) The stimulating tube was continually lowered around the top of the cupula and the

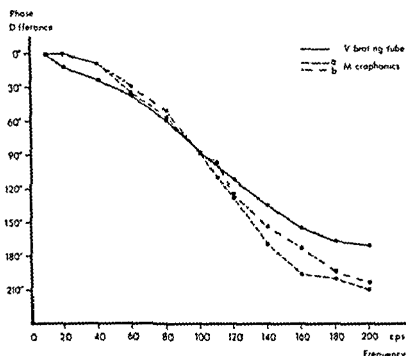


Fig. 43. Diagram showing the phase difference between the voltage driving the vibrator and the vibration amplitude, and between the same voltage and the microphonic potential in two different organs (*a* and *b*).

ment and not velocity in which case it would have been 90° ahead of the displacement of the tube at all frequencies.

b) *Transient Stimulation.* For the transient stimulus the impulse response of the vibrator was determined with the capacitance transducer and appears from Fig. 44 *a*, which shows the amplitude of the vibrator when a transient driving impulse was applied. The microphonic potential generated by the same transient stimulus appears from Fig. 44 *b*. Fig. 44 consequently illustrates the temporal relationship between the displacement of the stimulating tube and the microphonic output generated by this stimulus. It is seen that the microphonic potential follows the displacement of the stimulating tube and not the velocity. The extremes of each *wave of the damped oscillations correspond to a negative peak in the microphonic* potential. In the case of a transient stimulus the microphonic potential consequently is a measure of displacement and not velocity.

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between the generation of stimulus and the stimulation of the sensory cells and thus interfere upon the stimulus response relationship Kuiper (1956) stimulated the organ directly with a small magnet applied to the top of the cupula With the stimulating technique used in the present investigation the cupula is stimulated directly and an optimal transmission of the stimulus to the sensory cells can conveniently be assured throughout an experiment by adjusting the vertical position of the tube The frequency and the amplitude of vibratory stimulation is regulated with the oscillator and the variable atternuator, and the amplitude of static displacement with the manipulator or with a variable DC current Different directions of stimulation can be chosen by rotating the organ in relation to the stimulating tube With the stimulating technique developed an improved quantitative control of the stimulus is achieved

The Significance of the Recording Conditions

The recording conditions investigated concerned the position of the recording electrode in relation to the sensory epithelium and the influence of different volumes of fluid and of fluids of different conductivities on the microphonic output

Experimental conditions The organ was stimulated along the axis of the canal with a constant amplitude at a frequency of 100 cps and at optimal coupling between the stimulating tube and the cupula The microphonic output was recorded at different positions of the electrode along the canal and also in a position beneath the membranous tissue floor of the canal In the experiment illustrated in Fig 46 the ventral half of the cupula had been cut away slightly above the sensory epithelium and the stimulating tube was fitted to the remaining half of the cupula In this way it was made possible to move the tip of the electrode at a parallel course along the bottom of the canal and above the surface of the sensory epithelium With the electrode at a constant position at the rostral margin of the sensory epithelium the output was also recorded when distilled water or Ringer solution was substituted for the physiological canal lymph

Results The magnitude of the microphonic potential at different distances from the sensory organ appears from Fig 46 The microphonic output shows its maximum above the sensory epithelium and decreases continually with increasing distance Two mm away from the organ the output is about 20 per cent of what it is above it In the standard experiment the microphonic potential was picked up with the electrode close to the rostral margin of the sensory epithelium In spite of the decline of output at increasing electrode distance it had to be ensured that with the active electrode in its normal position a microphonic potential was not picked up also from the neighbouring organs To this end the organ normally recorded from was destroyed and the vibrations of the stimulating

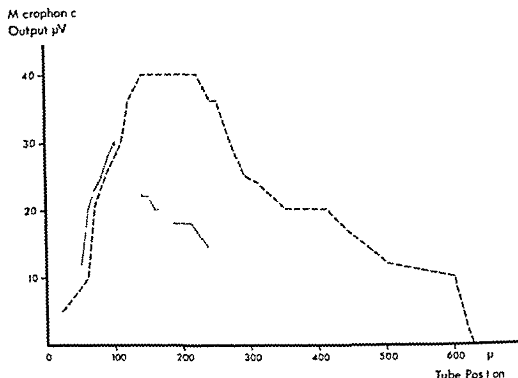


Fig. 4a. Diagram showing the magnitude of the microphonic potential at different vertical positions of the stimulating tube which is continually lowered around and pressing against the top of the cupula in one case in a fresh organ (— — —) and in the other after considerable experimentation ( ).

microphonic output was determined at different vertical positions of the tube.

Results. A microphonic response first appears when contact is established between the stimulating tube and the cupula (Fig. 45). When the stimulating tube is lowered, the output gradually increases until it reaches a maximum when the degree of coupling is optimal. Beyond this level the output decreases due to the excessive pressure applied to the cupula. The range of optimal output is about 100 µ in a fresh and successful preparation whereas in an organ which has been the subject of considerable experimentation the range of optimal coupling is much narrower (Fig. 45).

Conclusion. Whereas it is hazardous to judge only by visual control whether the stimulating tube is properly fitted to the cupula, this is conveniently established by simultaneous recording of the microphonic output.

Discussion. In earlier electrophysiological investigations the organ has generally been stimulated by steady or alternating water currents directed at the cupula (Sand 1937, Jielof et al. 1952, Görner 1963) or propagated through the surrounding water and via the tissues and the fluid of the canal to the sensory organ (Suckling and Suckling 1950, Harris and Bergeijk 1962). By these methods a series of mechanical events intervene

between the generation of stimulus and the stimulation of the sensory cells and thus interfere upon the stimulus-response relationship. Kuiper (1956) stimulated the organ directly with a small magnet applied to the top of the cupula. With the stimulating technique used in the present investigation the cupula is stimulated directly and an optimal transmission of the stimulus to the sensory cells can conveniently be assured throughout an experiment by adjusting the vertical position of the tube. The frequency and the amplitude of vibratory stimulation is regulated with the oscillator and the variable alternuator, and the amplitude of static displacement with the manipulator or with a variable DC current. Different directions of stimulation can be chosen by rotating the organ in relation to the stimulating tube. With the stimulating technique developed an improved quantitative control of the stimulus is achieved.

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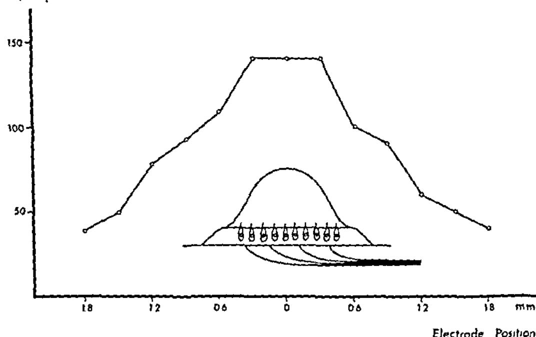


Fig 46 Magnitude of the microphonic potential at different recording positions along and parallel to the floor of the canal

tube were allowed to propagate in the canal fluid, or the vibrating tube was applied to the connective tissue at the floor of the canal With the recording conditions otherwise unchanged no activity could be recorded even when unduly high vibration amplitudes were used

There is a reversal of sign of the microphonic potential when the electrode is introduced beneath the thin membranous tissue sheath lining the floor of the canal (Fig 47). Also in this recording position the output is largest close to the sensory area The phase relations and the shape of the microphonic output are otherwise independent of the position of the electrode

The maximal microphonic output may vary from about 800 μV and downwards, depending on the recording conditions and on the general condition of the organ, but it is usually about 100–200 μV The output of an organ depends on the amount of canal lymph which surrounds the organ The microphonic potential is smaller when the canal is almost filled with fluid than when the level is kept lower The output increases when distilled water is substituted for the canal lymph and it decreases when Ringer solution is instead applied

Conclusion During one and the same experiment the recording conditions have to be kept constant, otherwise the microphonic output will vary

Discussion It appears that the microphonic potential has its origin in the sensory epithelium as was also concluded by Jielof *et al* (1952) That

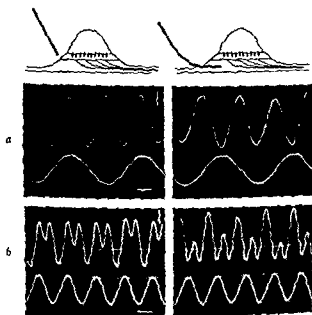


Fig 47 Appearance of the microphonic potential recorded in the normal position inside the canal and recorded from beneath the sensory epithelium in the case of (*a*) symmetric and (*b*) asymmetric output (*a* Time bar 2 msec, vibration amplitude 4 μ, vertical bar 20 μV *b* Time bar 5 msec, vibration amplitude 4 μ, static displacement 5 μ caudally, vertical bar 20 μV)

this is true in the organ of Corti has been shown by Bekesy (1932) and in the crista ampullaris by Trincker (1957)

The dependance of the amplitude of the microphonic output on the amount and the type of fluid surrounding the organ may be explained by the larger shunting effect of a large volume of fluid than of a small one and by the different conductivities of the fluids applied

Summary

The experiments hitherto described have been designed to investigate the character of the microphonic response and to study the influence on the microphonic potential of such factors which concern the stimulating technique and the methods of recording This investigation has been intended to provide a background for an appropriate experimental approach and an accurate interpretation of the experiments to be described in the following sections

The Input-Output Curve

This paragraph describes the quantitative relation between the [illegible] of the stimulus and the amplitude of the microphonic potential

Experimental conditions The choice of experimental conditions [illegible]

[illegible]

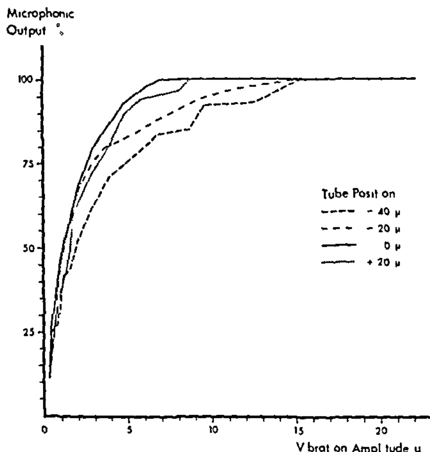


Fig. 48. Voltage of microphonic potential in per cent of maximal output plotted against vibration amplitude in microns. The different curves derive from the same organ but are obtained at different vertical positions of the stimulating tube above the sensory epithelium: 40 μ and 20 μ above the level of optimal coupling, at optimal coupling (0 μ) and 20 μ below this level.

termined by the experimental findings previously described. The organ was stimulated along the canal at a frequency of 100 cps. The input-output curve determined at optimal coupling between the stimulating tube and the cupula and also with different degrees of coupling. The vibration amplitude was continuously increased in steps of 0.1 μ or 1 μ and the amplitude of the microphonic output was simultaneously registered. The microphonic output measured is the peak-to-peak amplitude of a symmetric output showing no distortion of the sine wave shape.

In response to equal stimulation the microphonic output of different organs may vary considerably depending on the factors mentioned above even when stimulating and recording conditions are optimal. To enable comparison between the input-output characteristics of different recordings it is convenient to express the microphonic output in per cent of its maximal value, as will be done below.

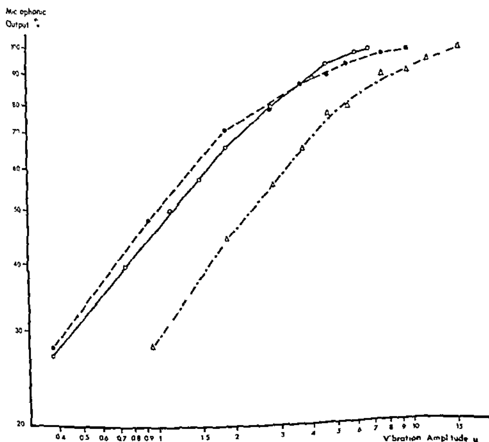


FIG 49 The input output curves of three different organs plotted in a double logarithmic diagram In two cases with normal cupulae (– – – —) in the other when the upper part of the cupula had been removed and the stimulus could be applied closer to the sensory cells (— ·– —)

Results When the microphonic output is plotted against the vibration amplitude it is found that the microphonic output increases in a non-linear fashion with increasing vibration amplitude (Fig 48) It increases faster at small vibration amplitudes than at higher ones, and at a certain amplitude it finally reaches a saturation value

The input output curve of different organs plotted on a double logarithmic scale, appears from Fig 49 It is seen that the curve is linear within a certain range of stimulating amplitude, above which the slope of the curve gradually decreases until the maximal output is reached Not only does the magnitude of the maximal microphonic output vary in different recordings, *but also* the vibration amplitude *at* which saturation is reached It appears from Fig 48 that the input-output relationship is intimately related *to the* degree of coupling between the vibrating tube and cupula In this experiment the stimulating tube was lowered 20 μ at a time

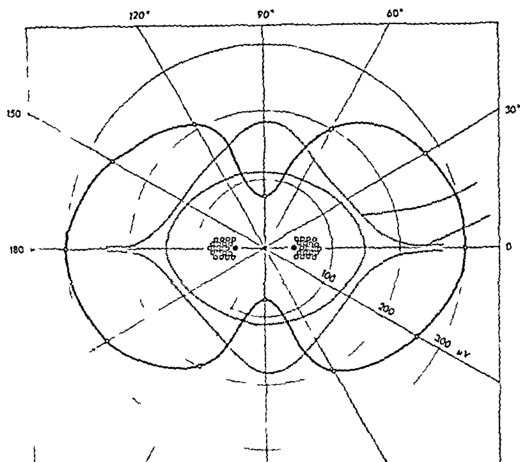


Fig. 50. The directional sensitivity of an organ illustrated in a polar coordinate system. At each direction of stimulation the microphonic potential is plotted on the appropriate coordinate. The axis of the canal is parallel to the coordinate 0°–180°. The outlines of the organ is indicated by the dotted line and the orientation of the two groups of hair cells within the sensory epithelium is indicated by two sensory hair bundles oriented with their kinocilia pointing in opposite directions. (Vibration amplitude 4 µ, frequency 100 cps.)

Results. The directional sensitivity of the organ is illustrated graphically in polar coordinates in Fig. 50. The output is largest when the direction of stimulation is parallel to the axis of the canal, and at gradually increasing deviation from this direction the output decreases until it reaches a minimum when the stimulating direction is perpendicular to the orientation of the hair cells.

Discussion. The theory proposed for the function of the hair cells in the lateral line canal organ (Flock and Wersäll, 1962 *b*) is based upon a directional sensitivity of the individual hair cell analogous to that found in the crista ampullaris (Lowenstein and Wersäll, 1959). This theory states that a displacement of the sensory hairs in a direction away from the stereocilia towards the kinocilium is excitatory and is followed by depolarization, i.e. a negative potential in the endolymph or canal lymph, and an increased

discharge frequency in the innervating nerve fibres. A displacement in the opposite direction causes hyperpolarization and inhibits the afferent discharge. The hair cells are consequently directionally sensitive and signal the direction of stimulation by a two way modulation of the sensory response. It follows by inference that a displacement in a direction perpendicular to the cell should be an ineffective stimulus.

As it appears from Fig. 30 the directional sensitivity of the organ approximately corresponds to the cosine function of the output generated at a stimulating direction along the axis of the canal, as would be the case if the stimulus which generates the microphonic potential is the component vector of displacement coinciding with the axis of the canal. In this diagram a pure cosine function would have yielded a figure of two circles touching at origo. There are two dissimilarities to explain: at deviating stimulating directions the output is larger than the cosine function and accordingly it is not zero at perpendicular stimulation. It is known from the electron microscopic investigation that while the hair cells are principally oriented parallel to the axis of the canal there is a random deviation of 10°–15° from the main orientation. For these cells a displacement which is perpendicular to the main orientation will still have a component vector which is an effective stimulus, if the directional sensitivity of the single hair cell is a cosine function. The dissimilarity between the recorded and the theoretical characteristics of the directional sensitivity of the organ may then be accounted for by overlapping of the angular responses of the individual hair cells.

It is stated by the theory that the signs of the potential shifts generated by the individual hair cell will be reversed when the cell is stimulated from opposite directions. While this is true for the individual hair cell the microphonic potential recorded from the lateral line organ is always negative ... stance which is explained irrespective of the ... by the presence of hair cells which are oriented in opposite ... towards the tail (see ... pointing alternatively towards the head or towards the tail (Sand 1937) as well as in the ... paragraph). In the lateral line canal organ (Sand 1937) ... is signalled in ... epidermal organ (Gorner 1963) the direction of stimulation ... of the resting dis... the innervating nerve fibres by a two way modulation ... is excitat... displacement ... charge frequency. Displacement in one direction is ... There are two groups of nerve fibres ... in the opposite direction is inhibitory ... site direction. Since there are two ...

wh...

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fibre must innervate hair cells ... 1963). Gorner h...

(Flock and Wersall 1962 b, Gorner 1963) ... largest when the stimulating direc... nerve fibre the afferent discharge rate is ... of the hair cells where ... it is only slightly ... tion is parallel to the orientation of ... when the direction of stimulation ... above the resting discharge frequency ... However he did not describe this direction perpendicular to this orientation.

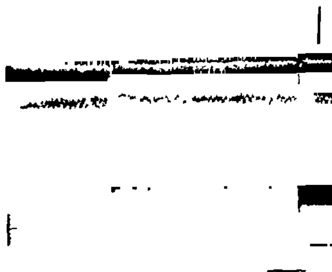


Fig. 53. Recording which shows the phasic tonic effect of sudden static displacement on the microphonic potential. (Time bar 0.2 sec. vibration amplitude 4 μ, static displacement 4 μ, vertical bar 200 μV.)

tude, the larger is the displacement required to cause a transition into a single frequency. In the preparation in Fig. 51 a displacement 2–3 times the vibration amplitude was necessary, in other cases 4, 6 or even 10 times is required. At rostral displacement the amplified negative peak is the one that corresponds to the rostrally directed swing of the tube, whereas at caudal displacement there is a phase shift of 180°, so that the amplified peak follows the caudal swing (Fig. 52). The phasic-tonic response of the organ appears from Fig. 53. When static displacement is suddenly applied the dynamic response is larger than the tonic response which shows comparatively little adaption. It is also seen that there is an off as well as an on response.

Discussion. The general theory proposed for the function of the hair cells in the acoustico-lateralis system states that a displacement in a direction away from the stereocilia towards the kinocilium, or in the cochlea towards the centriole, is excitatory and causes depolarization and increased discharge frequency in the innervating nerve fibres, while a displacement in the opposite direction is inhibitory and causes hyperpolarization and decrease of afferent discharge (Lowenstein and Wersäll, 1959; Flock and Wersäll, 1962 b; Flock *et al.*, 1962; Engström *et al.*, 1962, Dijkgraaf, 1963, Görner, 1963; Lowenstein *et al.*, 1964, Flock 1964, Wersäll and Flock, 1965). Accordingly the microphonic potential generated by the hair cell should follow the frequency of the stimulus. In the cochlea and in the crista ampullaris the hair cells are all oriented in the same direction, and in these organs the frequency of the microphonic effect is also equivalent to that

of the stimulus (Tasaki *et al*, 1954) In the cochlea the centriole of the outer hair cells is consistently facing in the radial direction, away from the tunnel of Corti (Held, 1926, Flock *et al*, 1962, Engström *et al*, 1962) Békésy (1953) has shown that the phase of displacement of a vibrating needle away from the modiolus yields depolarization while opposite displacement causes hyperpolarization In the crista ampullaris of the horizontal canal, a displacement of the cupula towards the utricle is excitatory (Lowenstein and Sand, 1940, Trincker, 1957) and this is also the direction in which the kinocilia face (Lowenstein and Wersäll, 1959) The microphonic effect of the lateral line canal organ has a frequency twice that of the stimulus (Jielof *et al*, 1952, Kuiper, 1956) In this organ there are two groups of hair cells which are oriented in opposite directions with their kinocilia pointing alternately towards the head or towards the tail (Fig 19) The microphonic effect recorded is the sum of the potentials generated by the two groups of cells and the double frequency would accordingly be accounted for by the superposition of the two antagonistic responses (Flock and Wersäll, 1962 *b*) Since a microphonic effect may at all be recorded, it is a prerequisite condition that the simultaneously generated potentials are not equally large, if that were the case they would cancel each other That it is depolarization that is larger than hyperpolarization is known from the fact that a transient displacement in either direction always evokes a negative potential (Fig 41) The theory consequently suggests at least for the lateral line organ, a non linearity of receptor function

The experimental results will be considered in relation to their theoretical explanation The explanation offered for the generation of the normal symmetric microphonic output is illustrated by Fig 54 J In this figure the input output transfer functions for two hair cells oriented in opposite directions are plotted in a linear coordinate system The absciss is the displacement of the cupula or of the sensory hairs, in either direction and the ordinate is the negative or positive receptor potential i e depolarization or hyperpolarization respectively The input is the oscillating displacement of the cupula at vibratory stimulation and is illustrated as a sine wave with the same absciss but with time as an ordinate The output is illustrated to the right with the microphonic potential on the ordinate and with time on the absciss

During the first half period of stimulation the cupula is displaced in the excitatory direction in relation to cell A and during this half period the response of cell A is a graded depolarization which is at each instance proportional to the displacement of the cupula The simultaneously evoked response of cell B is a hyperpolarization since this cell is oriented with its kinocilium pointing in exactly opposite direction During the next half period it is cell B that is subjected to excitatory displacement and cell A that is inhibited Since depolarization is always larger than hyperpolarization the microphonic output is composed by one negative peak at each half

has received another explanation. Sand (1937) observed that static displacement which inhibited the afferent discharge inhibited also the response to vibration in the innervating nerve fibres. It appears that the close relationship observed for the effect of static displacement on the microphonic potential is reflected by the impulse frequency in the nerve fibres.

If there is a greater population of cells which are excited at displacement towards the left than of such which are excited by displacement towards the right, the resulting output will show a partly suppressed second harmonic even at stimulation around the equilibrium position. If this asymmetry is compensated by shifting the bias towards the right, the wave shape of the calculated output will show a distortion as was also found in some organs (Fig. 42). A microphonic potential showing such distortion does not give an accurate measure of input output relations, neither does the peak to peak amplitude of a microphonic output which shows partial suppression of the second harmonic due to static displacement.

It appears from Fig. 54 that the amplitude of the negative peak will increase with increasing static displacement and that the second harmonic will disappear when the displacement is equivalent to the vibration amplitude. At increasing vibration amplitudes an increasing bias is needed to cause the disappearance of the second harmonic as confirmed in the experiments and as has been found also by Jielof *et al.* (1952) and by Kuiper (1956). In the experiment the bias required to cause a transition into pure single frequency was larger than the vibration amplitude, a circumstance which might be explained by a plastic tonic behaviour of the receptor, caused by a partial creeping back of the cupula due to its plasticity, or to adaption of the sensory cells. This conclusion is based on the experimental finding that the effect of static displacement is largest when it is initiated, whereupon it is somewhat diminished (Fig. 53). The tonic response however shows no or very little adaption. It is also seen that the receptor gives an off as well as an on response.

The amplification produced by static displacement corresponds to the superposition effect described by Jielof *et al.* (1952) and by Kuiper (1956). When instead of static displacement a low frequency vibration is superimposed on a high frequency vibration an amplification of the high frequency microphonics is caused in the negative phase of the low frequency response. The superposition effect consequently indicates the non linear function of the sensory cells.

The recorded microphonic effect is always the sum of simultaneous responses, and since intracellular recordings were not obtainable no experiment could be thought of by which the input-output function of the single hair cell could be separated from that of its oppositely oriented neighbour. In Fig. 55 the non linearity of the stimulus response transduction curve is represented in a linear scale by the sudden change of the slope of the curve along which depolarization and hyperpolarization is plotted for equal amplitudes of displacement in opposite directions. This representation of

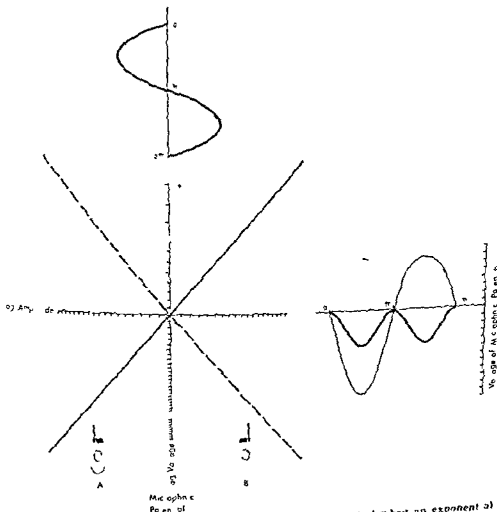


Fig. [illegible] Illustration of the generation of the microphonic potential when an exponential and input output transfer relationship is chosen. The amplitude of cupular displacement and the voltage of hyperpolarization and depolarization is plotted on logarithmic scales. For details see the text.

the non linearity is highly approximate and has been adopted for reasons of simplicity. A microphonic output reproduced from such a transducer function would actually show a *distortion* of the sine wave shape at stimulation around the equilibrium position and a precise reproduction of a sine wave stimulus when stimulation occurs at static displacement equal to or larger than the stimulating amplitude. However, according to the experimental findings this is not the situation (page [illegible]).

It is well known that biological events often obey logarithmic laws. The possibility that the stimulus response transfer function of the hair cell is also logarithmic was therefore taken into consideration. The theoretical diagram presented in the Figs [illegible] and [illegible] is a logarithmic coordinate system

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where the ordinate is the logarithm of the microphonic receptor potential above or below the resting potential, *corresponding to hyperpolarization* and depolarization respectively. The abscissa indicates the logarithm of displacement in either direction. The transduction curve of each cell is represented by a straight line passing through origo, and which is inclined towards right or left, depending on the orientation of the hair cell. In this case the hair cell is working on a continuous exponential curve the orientation of which is determined by the orientation of the cell. At cupular displacement of the same magnitude but in opposite directions the amount *of depolarization yielded by excitatory displacement is larger than that of* hyperpolarization caused by displacement in the opposite direction, and accordingly the non-linearity is accounted for. The input is the logarithm of a pure sine wave photographed from the oscilloscope and to the right the output voltage is plotted on a linear scale. It is seen from Fig. 55 that the microphonic receptor potential of each hair cell has a sinusoidal wave shape, but that the positive peak is broader than the negative peak. The wave shape of the summed microphonic output is not easily distinguished from a pure sine wave. When the cupula is given a bias and is vibrating outside the equilibrium position, the microphonic output will be gradually shifted into single frequency by abolition of the second harmonic (Fig. 56) which is completely suppressed when the bias corresponds to the amplitude of the vibration. At this bias the total output is amplified, and it is also noted that the aberration from the pure sine shape is conspicuously increased by flattening of the positive peak. On all appropriate photographs of the microphonic output when it has been transformed into single frequency by static displacement, wave shape was consistently found to diverge from the pure sine shape in the manner calculated from the logarithmic transfer function (Fig. 40 *b*). In the case of zero bias the recorded *output could not be distinguished from* a pure sine wave, provided that the vibration amplitude was not too large (Fig. 40 *a*).

It is consequently found that a logarithmic stimulus response function gives a wave shape representation which agrees with the true situation while this would not be the case if the transduction curve were an interrupted linear function. By the logarithmic function the non-linearity of the input-output relationship will be accounted for. Whether the stimulus response relationship illustrated in the Figs. 55 and 56 represents the true *input-output transfer function of the hair cell is subject to further analysis.*

Evidence exists suggesting a non-linear sensory response also in other organs belonging to the acustico-lateralis system, though the proof is not conclusive. *In the crista ampullaris* Trincker (1957) has shown that the degree of depolarization amounts to higher values than that of hyperpolarization caused by cupular displacement in the opposite direction. Ewald's well known second law (1892) states that in the horizontal canals the excitatory response to rotary stimulation must be larger than the inhibitory response simultaneously evoked from the opposite canal. In the

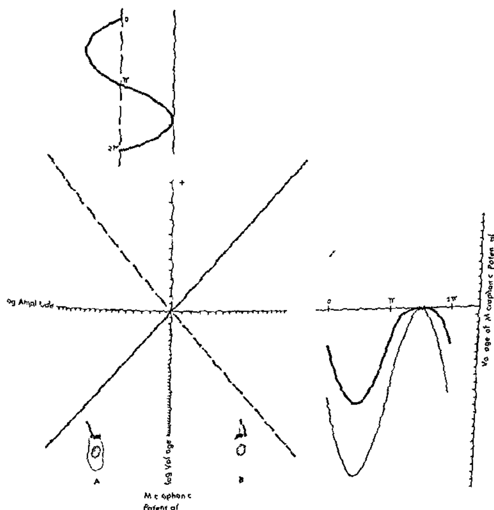


FIG 56 The theoretical effect of static cupular displacement of the same magnitude as the vibration amplitude illustrated for the situation of a stimulus-response relationship equivalent to that of the preceding figure For details see the text

crista ampullaris of the pigeon de Vries *et al* (1955) and Kuiper (1956) has also demonstrated a superposition effect of the microphonic potential It therefore seems that also in the crista ampullaris the sensory response is governed by a non linear function Whether this is the case also in the other organs belonging to the acustico lateralis system is a matter of future investigation

Measurements on the DC Potential Shift

These experiments were performed to demonstrate the DC response of the organ at vibratory stimulation

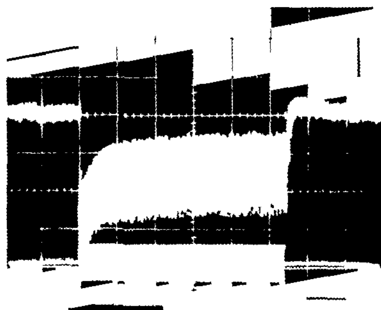


Fig. 57 Recording which illustrates the DC potential shift accompanying the microphonic potential (Time bar 0.2 sec vibration amplitude 4 μ, vertical bar [illegible] μV)

Results The organ was stimulated with 0.5–1 sec long pulses, within a frequency range of 100 cps to 1,000 cps. It was found that there is a negative DC potential shift superimposed upon the microphonic response (Fig. 57). The DC shift is largest at the beginning of stimulation where it is present at all frequencies studied, and is followed, at frequencies higher than 150 cps, by a steady negative potential. The magnitude of the potential change depends on the frequency as well as on the amplitude of the stimulus. Within a certain limit the steady negative shift increases *with the frequency and with the amplitude of the stimulus.*

Discussion The DC potential shift accompanying the microphonic output of the lateral line organ was first observed by Kuiper (1956). The potential change is always of a negative sign. In the cochlea a similar negative summating potential is observed but under certain conditions a positive summating potential may also be seen (Davis *et al.* 1958).

It appears from the preceding paragraph that as far as the pure microphonic potential is concerned the extremes of the positive peaks of the microphonics touch upon the base line indicating the level of the resting potential as long as the magnitude of static displacement does not exceed vibration amplitude (Figs. 54, 55, 56). The positive peaks will leave the base line and cause a DC potential shift to occur only when the inclination of the sensory hairs is larger than the vibration amplitude. Any superimposed static displacement will be revealed by a transition into the single frequency, and in the experiment it was ensured by watching the curve shape of the microphonic potential that there was no significant simultaneous static displacement of the cupula. It is concluded that the

negative DC potential observed is therefore not an effect related to a steady one way displacement of the cupula or the sensory hairs

In the cochlea potential changes of different signs are caused by static as well as by vibratory displacement in opposite directions (Tasaki *et al* 1954 Bekesy, 1953) and are believed to reflect bending of the sensory hairs in certain directions In the lateral line organ the electrical effects of vibratory and static displacement are also closely related to each other and are correlated in the same way to the directional sensitivity of the individual hair cell (page 70) Cupular displacement in the direction in which the kinocilium leads causes depolarization and displacement in the opposite direction causes hyperpolarization

It was stated by Davis (1959) that at intensities high enough to evoke the summating potentials some kind of mechanical rectifying or detector action takes place in the inner ear to cause an asymmetrical persistent one way bend in the hairs of certain cells The sustained bend of the hairs would act as a steady stimulus to the hair cells that are affected Just as the cochlear microphonic is the sign of a symmetrical vibratory bending of the hairs the negative summating potential would be the electrical sign of an asymmetrical rectified longitudinal shift *affecting the* inner hair cells Consequently the bending of the hairs is supposed to account for not only the cochlear microphonic but also for the summating potentials (Davis 1957 Davis 1961)

In the lateral line organ the stimulus response relationship of the hair cell is a non linear function at symmetric vibratory bending of the sensory hairs the amplitude of the negative half period is larger than that of the positive If these potential changes are integrated over time a *negative* potential shift will result It is suggested that *the DC potential* shift observed at symmetric vibratory stimulation in the lateral line canal organ is based on the non linearity of the input-output transfer function of the hair cell and is caused by the action of a cellular integrating mechanism which summates the alternating microphonic potential over time *Whether* similar potential changes occurring in other organs *belonging to the* acustico lateralis system might be accounted *for on* an analogous basis is a matter of future investigation

SUMMARY

An experimental technique was *developed* which allowed a quantitative study of the stimulus response *relationship* between a well calibrated stimulus of adjustable amplitude *and direction* and the microphonic potential

It was found that *it is of* significant importance that the wave shape of the microphonic potential is controlled at the beginning of each experiment

From phase measurements *between the movement* of the stimulating tube and the microphonics it was *concluded* that the microphonic potential ex

presses the amplitude and not the velocity of the stimulus, and it appears that the method of stimulation used provides an efficient direct transmission of the stimulus to the sensory cells. Whereas it is hazardous to judge only by visual control whether the stimulating tube is properly fitted to the cupula, this is accurately established by vertical adjustment of the position of the tube at simultaneous recording of the microphonics. The output may vary considerably depending on the position of the recording electrode in relation to the sensory epithelium and on the shunting capacity of the surrounding medium. It is therefore necessary to keep the recording conditions constant during one and the same experiment.

There was found to be a linear relationship between the vibration amplitude and the microphonic potential output when the input-output curve was plotted in a double logarithmic diagram. This is true within a range of vibration amplitude from about 0.4 μ to 3 μ. At higher vibration amplitudes the microphonic potential gradually reaches a saturation value. The recorded microphonic potential does not express the function of the individual hair cell but the sum of the two antagonistic responses generated by the two groups of hair cells oriented in opposite directions.

The directional sensitivity of the organ was determined by measuring the magnitude of the microphonic output at different stimulating directions. It was found that the output is largest when the direction of stimulation is parallel to the axis of the canal, and at gradually increasing deviation from this direction the output decreases until it reaches a minimum when the stimulating direction is perpendicular to the canal. Since the hair cells are oriented along the axis of the canal, it is concluded that the microphonic potential generated by the individual hair cell is proportional to the component vector of displacement along the orientation of the cell.

Experiments on the effect of static displacement were carried out in order to investigate the non-linearity of receptor function. For each hair cell cupular displacement in a direction away from the stereocilia towards *the kinocilium causes depolarization whereas displacement in the opposite* direction causes hyperpolarization. It was found that for the individual hair cell the amount of depolarization is larger than that of hyperpolarization caused by equally large displacements of the cupula in opposite directions. There is consequently a preponderance of depolarization over hyperpolarization which explains the finding that when the cupula is given a gradually increasing bias there is a gradual amplification of that negative peak of the microphonic potential which corresponds to the depolarized group of hair cells and a suppression of that peak which corresponds to the group of hair cells which are hyperpolarized by the given bias. On the basis of these findings it is concluded that the input-output transfer function of the individual hair cell is non-linear at least at vibration amplitudes larger than about 0.4 μ which was the smallest vibration amplitude at which a microphonic potential could be detected.

It was finally found that on vibratory stimulation there is a negative DC

potential shift superimposed upon the microphonic response. It could be established that this potential shift is not caused by a steady one way inclination of the sensory hairs. It is suggested that the DC potential shift observed is based on the non linearity of the input-output transfer function and is caused by the action of a cellular integrating mechanism when the alternating microphonic potential is summated over time.

General Conclusion

This paragraph is intended to give an abstract of the combined results of the electron microscopic and electrophysiological investigations and to give a review of the functional aspects discussed in relation to the findings. For this purpose the different structures of the sensory unit and their functional significance will be discussed in that sequence in which they are successively engaged in the process of sensory perception. The references and the discussions upon which the cited conclusions are based are to be found in the relevant paragraph. The results are also summarized at the end of each of the electron microscopic and electrophysiological sections.

The lateral line canal organs of fish are located in canals on the head and along the body of the animal. The sensory area is composed of mechanoreceptor cells enclosed by supporting cells forming a sensory epithelium innervated by the peripheral branches of the innervating nerve fibres. The sensory epithelium rests on an oval disc formed by branching nerve fibres and blood capillaries at the floor of the canal. From the top of each sensory cell a bundle of sensory hairs protrudes into a gelatinous cupula which rests on the sensory epithelium.

Movements of the fluid in the canal cause a displacement of the cupula which acts upon the hair cell through the sensory hairs. In response to stimulation the receptor mechanism of the hair cell is activated and regulates the flow of impulses in the innervating nerve fibre. The adequate stimulus for the sensory cells in the shearing displacement of the cupula in relation to the sensory epithelium. The response of the organ is determined by the mechanical properties of the cupula which is elastic as well as plastic. The cupular substance is secreted by the supporting cells which possibly contribute also to the formation of the canal lymph. The fibrillar cupular matrix is interwoven between the stereocilia a mechanical coupling which may serve the transmission of cupular displacement to the sensory cells.

The sensory hair bundle is composed of a number of stereocilia and one kinocilium located in the periphery of the bundle. The stereocilia act as levers which transmit the mechanical energy of the stimulus to the apical region of the hair cell where the rootlets of the stereocilia are planted in the cuticular plate. They are consequently engaged in the initial stage of the process of sensory perception in the hair cell which leads to the activation of the bio-electrical receptor mechanism.

As the result of the inclination of the sensory hairs a graded receptor potential is generated by the action of the hair cell. The receptor potential is an electrical potential shift which is proportional to the amplitude and not the velocity of cupular displacement. Vibratory stimulation causes an

alternating potential change, the microphonic potential which follows the frequency of the stimulus, and which is modified by sustained static displacement of the sensory hairs Whether static displacement alone causes a steady potential shift is not known in the lateral line organ but that is the case in the other organs belonging to the acousticolateralis system

The electrical energy of the microphonic potential is larger than the mechanical energy of the stimulus and the microphonic potential is therefore not a purely physical phenomenon but the electrical sign of a true biological sensory process which relies on the metabolic activity of the organ

The response of the hair cell is dependent on the direction from which the stimulus approaches the sensory hair bundle This directional sensitivity coincides with the morphological polarization of the hair cell indicated by the asymmetric position of the kinocilium in the sensory hair bundle An inclination of the stereocilia towards the kinocilium causes depolarization whereas an inclination of the stereocilia away from the kinocilium is followed by hyperpolarization At oblique stimulating directions the amplitude of the generated receptor potential is proportional to the component vector of displacement parallel to the rows of stereocilia It is conspicuous that the directional sensitivity of the cell is indicated by the position of the kinocilium and its asymmetric ultrastructure However the same correlation can be applied also to the stepwise increasing length of the stereocilia to the arrangement of the stereocilia and their rootlets, and to the structure of the cuticular plate At the present time it is difficult to judge upon which structure the directional sensitivity of the hair cell is dependent

At equally large displacements in opposite directions the amount of depolarization yielded is larger than that of hyperpolarization caused by displacement in the opposite direction The input output transfer function is therefore non linear at least at vibration amplitudes larger than 0 I μ

On vibratory stimulation there is a negative DC potential shift superimposed upon the microphonic response which is not caused by a steady one way inclination of the sensory hairs This DC potential shift would be accounted for on the basis of the non linearity of the input output transfer function if the alternating microphonic potential is summated over time by a cellular integrating mechanism

The hair cell is consequently provided with a receptor mechanism which registers the stimulus in terms of electrical potential changes The character of the stimulus is identified by the amplitude and by the sign of the receptor potential according to the amplitude and the direction of cupular displacement The nature of the receptor mechanism which governs the generation of the receptor potential is yet unknown and neither is it known with which structure it is associated

The hair cells are secondary sensory cells which are innervated by the peripheral branches of nerve fibres leading to the central nervous system A number of nerve endings make contact with the bottom of each hair cell

where both afferent and efferent nerve endings are recognized. At the afferent nerve ending synaptic transmission is initiated in an area which exhibits a specialized ultrastructural organization characterized by the presence of a synaptic bar surrounded by vesicles. The resemblance of these vesicles with synaptic vesicles favours the view of neurohumoral synaptic transmission at the afferent nerve ending. Each afferent nerve fibres contacts several hair cells, an arrangement which may serve to lower the treshold for initiation of an action potential by spatial summation of subliminal stimuli.

The afferent nerve fibres convey sensory information to the central nervous system by *a modulation of the resting discharge frequency*. Cupular displacement in a direction which causes depolarization is excitatory and leads to an increased discharge rate, while displacement in the opposite direction causes hyperpolarization which is inhibitory and is accompanied by a decreased impulse frequency. The sensory information represented by the receptor potential is subsequently reflected by the frequency of action potentials transmitted to the central nervous system by the afferent nerve fibres. The extent of deviation of the cupula from the normal position is signalled by the frequency level of afferent impulses. The exact relationship between the frequency of nerve impulses and the receptor potential at vibratory and static displacement remains to be investigated, and this is true also for the influence of the DC potential shift which accompanies the microphonic potential.

The efferent nerve endings innervating the hair cells are believed to represent an efferent feed-back system capable of modifying the peripheral sensory response.

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